Altered secretion of exosomes by muscle cells: role in ALS pathogenesis

Poster presentation with discussion

Saturday, June 20 2015

Ageing and dementia 1

P1101

Inflammation in frontotemporal lobar degeneration: cerebrospinal fluid signature of progranulin mutation carriers

D. Galimberti, R. Bonsi, C. Fenoglio, M. Serpente, S. Cioffi, G.G. Fumagalli, L. Ghezzi, A. Arighi, E. Scarpini
University of Milan, Ospedale Policlinico, Milan, Italy

Background and aims: Mutations in progranulin gene (GRN) are one of the major causes of autosomal dominant Frontotemporal Lobar Degeneration (FTLD). Progranulin displays anti-inflammatory properties and is a ligand of tumor necrosis factor receptor 2, expressed on microglia. A few cytokines and chemokines are altered in cerebrospinal fluid (CSF) from patients with sporadic FTLD, whereas no information is available in familial cases.

Methods or Materials or Case Report: To evaluate, through Bioplex, levels of 84 inflammatory molecules, including cytokines, chemokines, and related receptors, in CSF and matched serum, from patients carrying GRN mutations as compared with non-carriers and controls.

Results: Mean±SD Monocyte Chemoattractant Protein-1 (MCP-1) levels were significantly increased in CSF from sporadic FTLD patients as compared with controls (334.27±151.5 vs 159.7±49 pg/ml; P=0.01). In GRN mutation carriers versus controls, CSF levels of MCP-1 were unchanged, whereas Interferon-γ-inducible protein-10 (IP-10-CXCL10) levels were increased (809.17±240.0 versus 436.61±202.5 pg/ml; P=0.012). In the same group, Tumor Necrosis Factor (TNF)a and Interleukin (IL)-15 levels were decreased (3.18±1.41 versus 35.68±30.5 pg/ml; P=0.013 and 9.34±5.54 versus 19.15±10.03 pg/ml; P=0.023, respectively). Conversely, CCL-5 or regulated upon activation, normal T-cell Expressed, and secreted (RANTES) levels were decreased in patients, with or without mutations, as compared with controls (4.63±3.3 and 2.58±2 vs 87.57±70 pg/ml; P<0.05). Moreover, IP-10, IL-15 and RANTES CSF levels were not influenced by age, whereas MCP-1 levels increased with age (r=0.48; P=0.007).

Conclusion: These results demonstrate that different inflammatory molecules are de-regulated in CSF from patients with sporadic FTLD as compared with GRN FTLD, suggesting the existence of different inflammatory mechanisms possibly implicated in neuronal death.

Disclosure: Nothing to disclose

P1102

Physical activity as a predictor of clinical course in mild AD: the Danish Alzheimer's Intervention Study

K.S. Frederiksen[1], F. Waldorff[2], G. Waldemar[1]
[1]Danish Dementia Research Centre, Dept. of Neurology, Rigshospitalet, Copenhagen, Denmark, [2]The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Background and aims: Alzheimer's disease (AD) is associated with cognitive and functional decline. Moreover, neuropsychiatric sympotms such as apathy and anxiety are common. The objectives were to examine whether baseline physical activity was associated with global cognition, neuropsychiatric symptoms, quality of life (QoL), and activities of daily living (ADL) function at 12-month follow-up.

Methods: Data from the Danish Alzheimer's Intervention StudY (DAISY) were used. Patients had recently diagnosed mild (MMSE>20) AD. Baseline physical activity level was assessed by questionnaire. Proxies rated patients physical activity level as "no physical activity","less" or ">4 hours" per week. At 12-month follow-up, global cognitive function was assessed using MMSE, QoL using QoL-AD and Euro-QoL-5D VAS (EQ-5D VAS), neuropsychiatric symptoms with NeuroPsychiatric Inventory Questionnaire (NPIQ) and ADL with Alzheimer's Disease Cooperative Study-ADL scale (ADCS-ADL). 12-month follow-up scores were analysed in linear regression analysis (covariates: baseline MMSE, gender, age, group-allocation).

Results: In total 327 patients (Age (mean, SD): 76.2, ±7.2; gender f/m: 177/151; MMSE (mean, SD): 24.0, ±2.6) were included.Significant associations were found for EQ-5D VAS (β: 16.07; SE: ±3.49; p<0.0001) and for QoL-AD (β: 4.33; SE: ±1.09; p<0.0001). For NPI-Q a lower score (β:-1.88; SE: ±0.80; p=0.021) indicating fewer neuropsychiatric symptoms in physicially active patients, was found. Finally, being physically active was associated with better ADL function (β: 9.55; SE: ±2.78; p=0.001).

Conclusion: Physical activity predicts better functional level in 4 of 5 outcomes at 12-month follow-up in the early phase of AD.

Disclosure: Nothing to disclose

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Impact of physical activity on nursing home placement and mortality in mild Alzheimer's disease: the Danish Alzheimer's disease Intervention StudY (DAISY)

K.S. Frederiksen[1], F. Waldorff[2], G. Waldemar[1]
[1]Danish Dementia Research Centre, Dept. of Neurology, Rigshospitalet, Copenhagen, Denmark, [2]The Research Unit for General Practice and Section of General Practice, , Department of Public Health, University of Copenhagen, Copenhagen, Denmark, Copenhagen, Denmark

Background and aims: Alzheimer's disease (AD) is associated with increased mortality rates and increased risk of nursing-home placement, compared to age-matched healthy elderly subjects. Several factors, such as comorbidities may be contributing factors. In the present study we investigated whether physical activity may be associated with lower mortality rates and risk of nursing-home placement in patients with mild AD.

Methods: Data from the Danish Alzheimer's Intervention StudY (DAISY) were used. All patients had recently diagnosed mild (MMSE>20) AD. Physical activity level at baseline was assessed by questionnaire. Patients were followed for 3 years. Data on all-cause mortality and nursing-home placement were collected. Cox proportional-hazard regression analysis with mortality and nursing-home placement as outcomes and physical activity level as dependent variable was carried out. Covariates were social participation, Carlston Comorbidity Index, ADL function (Alzheimer's disease cooperative study – Activities of daily living scale) disease-specific Quality of Life (Quality of Life – Alzheimer's disease scale) and MMSE at baseline, age and gender.

Results: In total 327 patients (Age (mean, SD): 76.2, ± 7.2; gender f/m: 177/151; MMSE (mean, SD): 24.0, ±2.6) had data on proxy-rated physical activity levels available, and were included.

There were no significant associations between physical activity and mortality or nursing-home placement, although survival curves indicated a separation of the two groups (see figure 1 and 2). Survival curves for nursing-home placement indicated the largest separation.

Figure 2: Kaplan-Meier curve of probability of progression to nursing-home placement

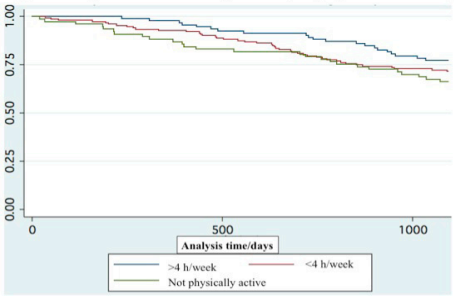
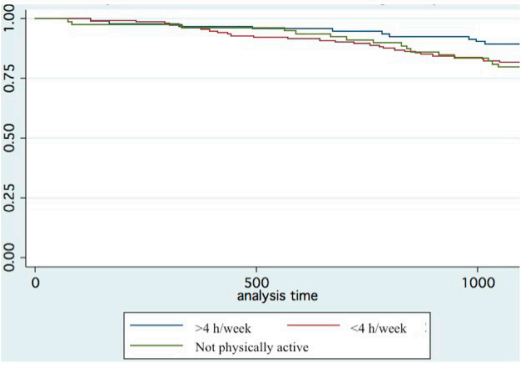


Figure 1: Kaplan-Meier curve of probability of progression to death



Conclusion: Several factors may contribute to mortality and risk of nursing-home placement in patients with mild AD. Being physically active may not reduce mortality or nursing-home placement.

Disclosure: Nothing to disclose

P1104

Quantitative EEG applying the statistical recognition pattern method: a useful tool in the dementia diagnostic work-up.

P. Høgh[1], K. Engedal[2], J. Snaedal[3], V. Jelic[4], B.B. Andersen[5], M. Naik[6], L.O. Wahlund[4], A.R. Øksengaard[4]

[1]Copenhagen University Hospital, Roskilde, Memory Disorders Research Unit, Dept of Neurology, Roskilde, Denmark, [2]Norwegian Advisory Unit for Ageing and Health,, Vestfold Health Trust, Oslo, Norway, [3]Landspitali - National University Hospital, Reykjavik, Iceland. , Ophthalmology, Reykjavik, Iceland, [4]Center for Alzheimer Research, Karolinska Institute, Section for Clinical Geriatrics, NVS Department, Stockholm, Sweden, [5]Danish Dementia Research Cente, Neurology, Copenhagen, Denmark, [6]Deakoness Hospital, Department of Geriatric Medicine, Bergen, Norway

Background and aims: The aim of the study was to examine the discriminatory power of the quantitative EEG (qEEG) applying the statistical pattern recognition (SPR) method to separate Alzheimer's Disease (AD) patients from elderly persons without dementia and from other dementia patients.

Methods: Participants were recruited from six Nordic memory clinics, 372 unselected patient, mean age 71.7 (s.d. 8.6), 54% women and 146 healthy old people, mean age 66.5 (s.d. 7.7), 60% women. After a standardized and comprehensive assessment clinical diagnoses were made according to international accepted criteria by at least two clinicians. EEG was recorded in a standardized way and analyzed independently of the clinical diagnoses using the SPR method.

Results: In receiver operating characteristic (ROC) analyses the qEEG separated AD from healthy old persons with an area under the curve (AUC) of 0.90, representing sensitivity (SS) of 84% and specificity (SP) of 81%. The qEEG further separated patients with Lewy body dementia or Parkinson's disease dementia from AD with AUC of 0.9, SS 85% and SP 87%.

Conclusion: The qEEG using the SPR method could be a useful tool in the dementia diagnostic work-up.

Disclosure: Nothing to disclose

P1105

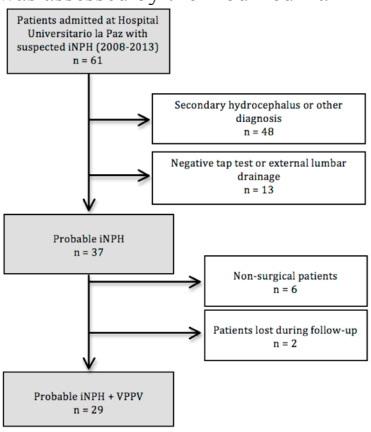
Long-term follow-up of idiopathic normal pressure hydrocephalus treated with ventriculo-peritoneal programmable valve

I. Illán-Gala, J. Pérez-Lucas , A. Martín-Montes, J. Máñez-Miró, G. Ruiz-Ares, E. Díez-Tejedor

Hospital Universitario La Paz, Neurology department and Stroke center, Madrid, Spain

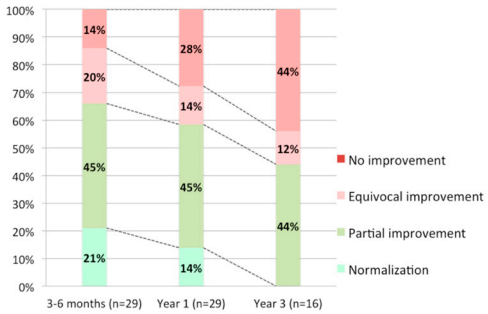
Background and aims: Idiopathic normal pressure hydrocephalus (iNPH) is considered a treatable cause of dementia. We aimed to study the frequency of the diagnosis and surgery-related complications as well as clinical and functional outcomes in a cohort of patients with iNPH treated with ventriculo-peritoneal programmable valve (VPPV).

Methods: Observational cohort study of patients diagnosed of probable iNPH and shunted between 2008 and 2013 in a neurosurgical reference center. We studied demographic data, vascular risk factors, symptoms at diagnosis and neuroimaging. Clinical improvement was classified in four categories (normalization, partial improvement, equivocal improvement and no improvement) and the functional level was assessed by the modified Rankin scale (mRS).

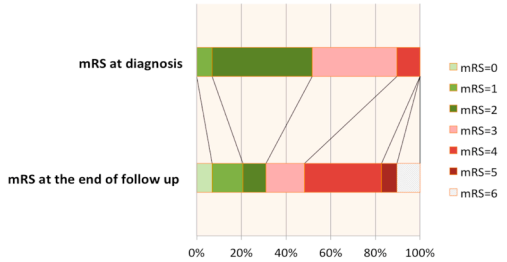


Sample selection

Results: 29 patients were included (5.4 cases per million per year) with a mean follow-up time of 37.8 months. The mean age was 73.9 years, 62.1% were male and 65.5% had hypertension. Clinical improvement (complete or partial) was observed in 58% after one year and in 48% at the end of the follow-up. The age, the presence of hypertension and the occurence of surgery-related complications were higher in the group with poor symptomatic response at first year. One patient died, 20.7% suffered from severe complications and 69% were dependent (mRS $\geq$ 3) at the end of follow-up. Age at diagnosis was independently associated with worse clinical response at one year and increased dependence at follow-up.



Symptomatic outcome after 6 months, one year and three years of VPPV placement



Comparison between functional level at diagnosis and at the end of the follow-up.

Conclusion: Symptomatic benefit of VPPV was partial and transient, with a high frequency of complications and bad functional outcome in long-term follow-up especially in the oldest patients.
Disclosure: Nothing to disclose

P1106

Have opioids replaced antipsychotics in the treatment of behavioural symptoms in dementia?

C. Jensen-Dahm[1], A. Nørgaard[1], C. Gasse[2], G. Waldemar[1]
[1]Danish Dementia Research Center, Copenhagen, Denmark, [2]National Centre for Register based Research, Aarhus, Denmark

Background and aims: Antipsychotics are often prescribed to treat neuropsychiatric symptoms (NPS) in dementia, but have been associated with serious adverse events and increased mortality, which has led to safety regulations worldwide. Recently it has been suggested that opioids may be used to treat NPS (Husebo BMJ 2011). The aim of this study was to investigate time trends of antipsychotic and opioid drug use in patients with dementia in Denmark from 2000-2013.
Methods : Population-based observational study with time series of cross-sectional studies and conducted by use of Danish nationwide registers including the entire elderly population (age≥65) of Denmark. The registers were used to identify patients with dementia and identify users of opioids and antipsychotics from 2000 to 2013.
Results: From 2000 to 2013 prevalence of antipsychotic drug use among patients with dementia decreased by 35.8% (from 31.3% to 20.1%), but during the same period opioids increased by 37.9% (from 24.2% to 33.8%) (figure 1). Among elderly without dementia antipsychotic drug use decreased by 37.8% (from 4.5% to 2.8%) and opioid use increased by 15.4% (from 14.9% to 17.2%) (figure 2).

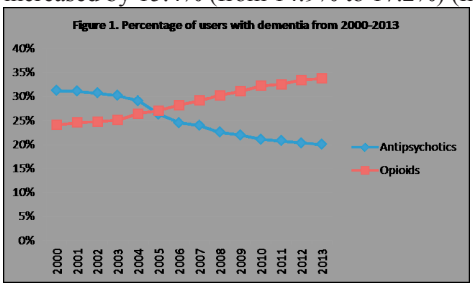


Figure 1

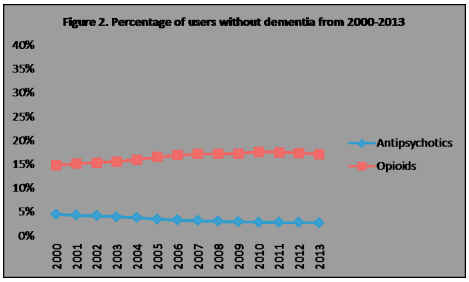


Figure 2

Conclusion: From 2000 to 2013 the use of antipsychotics among patients with dementia decreased, but during the same period use of opioids increased. The marked increase could be explained by a higher awareness among physicians of the importance of sufficient pain treatment. However, the high use of opioids is concerning and the association with a decrease in antipsychotics suggest that opioids may be used for managing NPS and to some extent have replaced antipsychotics.
Disclosure: Nothing to disclose

P1107

Altered default mode network connectivity during visual processing in patients with mild cognitive impairment (an fMRI study)

L. Krajcovicova[1], M. Barton[2], N. Elfmarkova[1], M. Mikl[2], R. Mareček[2], I. Rektorova[1]
[1]CEITEC - Central European Institute of Technology, Masaryk University, Brno, Czech Republic, Applied Neuroscience Research Group, Brno, Czech Republic, [2]CEITEC - Central European Institute of Technology, Masaryk University, Brno, Czech Republic, Multimodal and Functional Imaging Research Group, Brno, Czech Republic

Background and aims: The default mode network (DMN) is characterized by continuous activity during the resting state that decreases during goal-directed tasks. The object of our study was to detect specific alterations in DMN connectivity when switching from baseline to task condition (here the visual task) in 17 patients with mild cognitive impairment (MCI) as compared to 18 healthy controls (HC) and 15 patients with Alzheimer's disease (AD) using psychophysiological interactions (PPI) analysis.

Methods: The fMRI protocol (a complex visual scene-encoding task) was performed using a 1.5 T Siemens Symphony scanner. PPI analysis was used to assess the effect of the visual task on connectivity with the posterior cingulate/precunes (PCC/P, i.e. the posterior DMN node). Age, gender, education and a measure of atrophy were used as covariates.

Results: When switching to task, HC showed decreased DMN connectivity with the left middle temporal /middle occipital gyrus (MTG/MOG) and PCC/P bilaterally while MCI showed decreased DMN connectivity with bilateral precuneus only. Comparing HC and MCI resulted in a significant difference in the PPI effect in the right superior temporal gyrus (STG) and this difference became stronger in AD. In addition, MCI subjects as compared to AD group showed significant differences in bilateral precuneus.

Conclusion: We have found specific disturbances in connectivity between the DMN and the ventral visual pathway in MCI patients during the visual processing. These changes were more pronounced in AD patients.

Disclosure: The study was supported by the project "CEITEC - Central European Institute of Technology" (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund and by the project of specific research LF MU Brno no. 0975/2013

P1108

Following the spreading of brain structural changes in Alzheimer's disease: a longitudinal, multimodal MRI study

D. Mattavelli[1], F. Agosta[1], M. Weiler[1], E. Canu[1], M. Copetti[2], G. Magnani[3], A. Marcone[4], E. Pagani[1], M. Balthazar[5], G. Comi[3], A. Falini[6], M. Filippi[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neuroscience, Milan, Italy, [5]University of Campinas, Laboratory of Neuroimaging, Campinas, Brazil, [6]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: Longitudinal studies combining volumetric and diffusion tensor (DT) MRI measures may contribute to clarify the network-based degeneration model of Alzheimer's disease (AD). This study investigated grey matter (GM) atrophy and white matter (WM) tract damage progression in AD.

Methods : T1-weighted and DT MRI from 14 patients with probable AD were obtained at baseline and after a 16±3 month period. At baseline, CSF samples from patients and MRI from 37 controls were also acquired. Regional GM volume loss and DT MRI metrics from the interhemispheric and major long-association WM tracts were obtained. MRI metrics were compared between patients and controls, and changes over time were evaluated in patients.

Results: At baseline, patients showed cortical atrophy in the medial temporal and parietal regions and WM damage to corpus callosum, cingulum and inferior (ILF) and superior longitudinal (SLF) fasciculi bilaterally, and left uncinate relative to controls. During follow up, AD patients showed a progression of WM damage to the corpus callosum, SLF bilaterally, left ILF and right cingulum, while no GM atrophy was detected compared to baseline. Patients with higher baseline cerebrospinal fluid total tau showed greater WM integrity loss at follow up.

Conclusion: In AD, WM tract damage progresses over time and is likely to be driven by non-Aβ processes. The different temporal dynamics of GM and WM changes in AD suggest that DT MRI may provide additional markers to monitor disease progression.

Disclosure: Italian Ministry of Health (#GR-2010-2303035).

Cerebrovascular diseases 1

P1109

Does the side of stroke determine the side of pneumonia?

P. Alves[1], C. Silva[1], J. Baptista[2], B. Lima[3], M. Jacinto[4], A.C. Fonseca[1]

[1]*Centro Hospitalar Lisboa Norte - Hospital de Santa Maria, Neurology, Lisbon, Portugal,* [2]*Hospital Fernando da Fonseca, Infectious diseases, Lisbon, Portugal,* [3]*Hospital Curry Cabral, Infectious diseases, Lisbon, Portugal,* [4]*Hospital do Espírito Santo, Internal Medicine, Évora, Portugal*

Background and aims: Pneumonia is a frequent complication after stroke. Previous studies using ultrasonographic, radiographic and plethysmographic methods have demonstrated an alteration of diaphragmatic excursion on the side of paresis.

We aimed to determine if there is an association between the paretic side and the laterality of pneumonia after stroke.

Methods: A retrospective analysis of a consecutive cohort of patients admitted to a stroke unit from 2008 to 2014 was performed. Patients with the diagnosis of acute stroke and pneumonia were included. The laterality of pneumonia was determined through blinded-observation of chest x-rays by two researchers and, in case of disagreement, by a third one. The exclusion criteria were: absence of/or bilateral paresis; lack of radiological evidence of/or bilateral pneumonia; absence of concordance on pneumonia laterality by at least two observers; and bilateral encephalic lesions. Fisher's exact test was applied to study the association between the side of paresis and pneumonia.

Results: 88 patients were included. The median age was 69 years. 56% (n=49) had an ischemic stroke and 44% (n=39) a brain haemorrhage. 53% (n=47) presented right side paresis. The pneumonia was considered to be in the right side in 86% (n=76) with a Kappa value of interobserver concordance for laterality of 0.39. No significant statistic association was found between the side of paresis and pneumonia in included patients (p=1.0) and in the subgroups of patients with ischaemic stroke (p=0.67) or haemorrhagic stroke (p=1.0).

Conclusion: No association was found between the side of pneumonia and paresis. The predominance of right-sided pneumonia probably results from aspiration events.

Disclosure: Nothing to disclose

P1110

Axial myoclonus after ischaemic stroke

P. Alves, M. de Carvalho, R. Peralta, R. Geraldes, A.C. Fonseca, T. Pinho e Melo

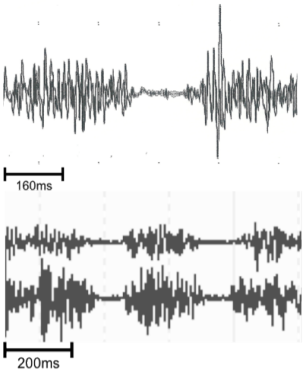
Centro Hospitalar Lisboa Norte - Hospital de Santa Maria, Neurology, Lisbon, Portugal

Background and aims: Myoclonus is a rare manifestation of stroke. The most common are asterixis, a subtype of negative myoclonus, after thalamic lesions. There are no reports of axial muscles myoclonus after stroke.

Case Report: A 67-year-old female was admitted due to decreased muscular strength and numbness on her left side of sudden onset. She had a past medical history of rheumatic atrial fibrillation not effectively anticoagulated with warfarin and an ischaemic stroke one year before with mild left appendicular ataxia and left upper limb hypoesthesia as sequelae.

At admission, neurological examination disclosed hemiparesis, severe superficial hypoesthesia and appendicular ataxia on the left side. The diagnosis of acute ischemic stroke was made and alteplase was administered. After being upraised, eight hours following endovenous thrombolysis, marked postural instability due to apparent sudden reduction in the cervical and dorsal axial muscle tonus was noticed. Magnetic resonance imaging revealed acute ischaemic lesions in the right thalamo-capsular and hippocampal areas. Electromyography recording disclosed negative myoclonus in the left upper limb and right paraspinal muscles and both negative and positive myoclonus in left paraspinal muscles (figure). No epileptic activity was observed on electroencephalography.

During follow up, there was a progressive improvement of the neurological deficits, including postural instability. After three months myoclonus were no longer present without any specific treatment.



Electromyographic recordings of right deltoid (top), right D5 paraspinal (middle) and left D5 paraspinal dorsal muscles (bottom) showing periods of muscular atonia with 100-150ms of duration.

Results: The temporal association between the appearance and the evolution of myoclonus and the other neurological deficits supports a causal relationship.

Conclusion: To our best knowledge this is the first report of axial myoclonus after stroke.

Disclosure: Nothing to disclose

P1111

Microbleeds: not more hemorrhagic transformation after thrombolysis

M. Annan[1], J.-P. Cottier[2], M. Gaudron[1], M. Dejobert[2], B. De Toffol[1], S. Debiais[3]

[1]CHRU Bretonneau, Neurology, [2]CHRU Bretonneau, radiology, [3]CHRU Bretonneau, neurology, Tours, France

Background and aims: Microbleeds (MB) are suspected to increase the hemorrhagic risk after thrombolysis for ischemic stroke (IS), but their exact significance is unclear. New imaging methods such as susceptibility weighted imaging (SWI) are more efficient to detect these MB. The main aim of this study was to look for a link between MB and hemorrhagic transformation after thrombolysis for IS.

Methods: This study was conducted prospectively between June 2012 and June 2013 in our stroke unit of Tours, France. All patients treated with intravenous thrombolysis for IS within 4.5 hours after onset of symptoms, and with a 3Tesla Magnetic Resonance Imaging (3T MRI) as first imaging were included. MB were counted on SWI according to BOMBs classification proposed by Cordonnier et al. in 2009. Hemorrhagic transformation were evaluated on SWI on a second MRI performed 7±3 days later according to the European Cooperative Acute Stroke Study (ECASS) classification.

Results: A total of 91 patients were included. Among them, 28 (30.7%) had MB on the first MRI. 17 (61%) patients with MB had HT, of which 2 (7%) were symptomatic. Those rates were respectively of 53% and 10% in patients without MB. The difference was not significative, the odd ratio (OR) was 1.43(0.56-3.65) for all-type of HT, and 0.65(0.12-3.47) for symptomatic HT.

Conclusion: In our study, MB detected with SWI are not significantly correlated to the risk of HT after thrombolysis. SWI increase detection of bleeding, such as MB or HT. Using SWI for the detection of both MB and HT is new in the literature.

Disclosure: Nothing to disclose

P1112

Blood rheology and endothelial dysfunction in acute ischemic stroke

M. Azhermacheva[1], V.M. Alifirova[1], P.D. Plotnikov Denis[1], O. Aliev[2]

[1]Siberian State Medical University, Department of neurology and neurosurgery, Tomsk, Russian Federation, [2]Federal State Budgetary Scientific Institution "Research Institute of Pharmacology and Regenerative Medicine named after E.D. Goldberg", Tomsk, Russian Federation

Background and aims: To assess endothelial dysfunction and blood rheology in acute ischemic stroke (IS).

Methods: The study included 49 patients with acute IS (age 64.5±12 years, mean±SD) and 20 control patients (56.3±4.7 years). High-resolution ultrasonography (TOSHIBA XCARIO SSA-660A) was used to measure intima-media thickness (IMT) and brachial artery (BA) diameters at rest and following 5 min of forearm occlusion. BA reactivity (brachial artery flow-mediated vasodilation (FMD) and glyceryl trinitrate (GTN)-mediated-dilatation) was assessed by method of D. Celermajer in 15-17 day of stroke. Hemorheological indexes were assessed in the first 12 hours and 8-20 day of stroke. All patients with acute stroke were treated legis artis.

Results: Significantly detected a difference IMT in patients with stroke (0.72±0.19) and in control group (0.6±0.13, $p<0.05$). BA diameters in rest in patients with stroke (3.80±0.13) were higher than in control group (3.61±0.20, $p<0.05$). Assessing of endothelial dysfunction was found the decreasing of FMD and the increasing of GTN-mediated-dilatation. Coefficient of endothelial dysfunction (GTN-mediated dilatation/FMD) was significantly higher in patients with acute IS (2.60±0.21) than in control group (1.45±0.19). Patients in the acute phase of IS had significant changes in hemorheological parameters which can be described as hyperviscosity syndrome: increased whole blood and plasma viscosity, plasma fibrinogen concentration, aggregation of erythrocytes and decreased red blood cell deformability. The strong correlations ($r>0.86$) between blood rheology indexes, brachial arterial reactivity and IMT were revealed.

Conclusion: In spite of the treatment, patients in acute IS had severe endothelial dysfunction and significant changes in hemorheological parameters.

Disclosure: Nothing to disclose

P1113

Changes in etiology and vascular burden of first ever Polish stroke patients from 1995 to 2013.

J. Bembenek, M. Karliński, A. Baranowska, A. Czlonkowska
Institute of Psychiatry and Neurology, [2]nd Department of Neurology, Warsaw, Poland

Background and aims: Our aim was to investigate long-term changes in profile, vascular risk factors and pre-stroke management in Polish patients with acute stroke.

Methods: This is a retrospective registry-based analysis of consecutive acute stroke patients from a highly urbanized area (Warsaw, Poland) admitted to a single stroke center between 1995 and 2013. A total of 4770 patients were divided to time periods: 1995-1999 (n=529), 2000-2004 (n=1253), 2005-2009 (n=1320) and 2010-2013 (n=871).

Results: The proportion of ischaemic strokes (88.2% to 90.9%) and male patients (45.2% to 46.2%) remained stable throughout the study period. Patients became older (from 72 to 76 years), more burdened with pre-existing hypertension (from 61.1% to 72.8%) and less often without pre-existing disability (84.3% to 67.4%). There was an increase in pre-stroke use of antihypertensives in patients with hypertension (from 77.8% to 90.5%), antiplatelets in patients with coronary artery disease (from 33.9% to 56.5%), vitamin K antagonists in patients with atrial fibrillation (from 6.3% to 39.8%) and statins (from 7.6% to 26.3%). Baseline stroke severity has decreased (from 9 to 6 points on the National Institutes of Stroke Scale) as well as the proportion of strokes due to small-vessel disease (from 22.0% to 8.3%).

Conclusion: Over the last two decades the profile of Polish stroke patients has changed significantly. Their increasing age and better management of pre-exisitng vascular risk factors were accompanied by decreasing baseline deficit and lower proportion of strokes attributed to small-vessel disease.

Disclosure: Nothing to disclose

P1114

TIA hits at younger age in low income areas within one city - the Budapest Districts 8-12 Project

D. Bereczki[1], A. Ajtay[2], I. Vastagh[2], I. Szőcs[2], A. Folyovich[3]
[1]Budapest, Hungary, [2]Semmelweis University, Department of Neurology, Budapest, Hungary, [3]Szent János Kórház, Department of Neurology and Stroke, Budapest, Hungary

Background and aims: Transient ischemic attack – TIA – is a major risk factor for stroke needing urgent evaluation. It is known that stroke appears at younger age in socioeconomically deprived regions. We test whether this age difference also exists for TIAs by comparing the least and the most wealthy of the 23 districts of the Hungarian capital city of Budapest.

Methods: We analyzed the database of the National Health Insurance Fund for patients living in the least (districts 8) and the most wealthy (district 12) regions, a population of 130,000 inhabitants, with the ICD-10 diagnosis of G45 established by any specialists in the inpatient or outpatient settings in the period of 2002-2007.

Results: Overall 4667 patients were diagnosed with TIA in the study period. Of the patients 35.4% were hospitalized for any reason. The diagnosis of TIA was assigned without neurological examination in 23.5% of the cases. Mean age of patients with the diagnosis of TIA was 4 years younger in the less wealthy district (61.9 vs. 65.9 years, $p<0.01$).

Conclusion: In the Hungarian healthcare system two-thirds of the patients with the diagnosis of TIA are treated in the outpatient setting, one out of 4 is not evaluated by neurologists, and patients are significantly younger in less wealthy areas. Socioeconomic deprivation is associated with younger age at disease onset not only for strokes but also for TIA. To achieve more efficient secondary prevention, healthcare policy should give higher preference for TIA patients in middle income countries, focusing on low-income regions.

Disclosure: Nothing to disclose

P1115

Locked-in syndrome after traumatic basilar artery dissection - a case report

T. Bourinaris, D. Kiourtidis, J. Rudolf, T. Tsironis, I. Tsiptsios
Thessaloniki, Greece

Background and aims: Basilar artery dissection is an unusual presentation of ischemic stroke. The event is either spontaneous or traumatic resulting in acute or delayed dissection. We report a case of a 46-year-old male presenting with locked-in syndrome, caused by multiple ischemic infarcts due to a traumatic basilar artery dissection.

Methods: A 46-year-old man was presented at the emergency department following a head trauma caused by a fall from a bike. At presentation the patient was stuporous without focal neurological signs, but was eventually intubated because of deterioration of his level of consciousness. An emergency brain CT scan revealed a linear stress fracture of the posterior wall of the sphenoid sinus. A brain MRI showed extended ischemic infarcts in occipital lobes, thalami, pons, medulla oblongata and left cerebellar hemisphere, while the MRA that followed revealed a distal basilar artery dissection.

Results: After extubation the patient had locked-in-syndrome with spastic quadriplegia, ophtalmoplegia and loss of brainstem reflexes, while retaining and communicating by eye blinking. A detailed workup excluded any other possible causes of the infarcts. Follow-up neuroimaging with intracranial MRA one month later confirmed the diagnosis showing eventual restoration of blood flow at the basilar artery.

Conclusion: Isolated traumatic basilar artery dissection is a rare event, since the concomitant involvement of the vertebral arteries is usually reported. This case is unique for the absence of major skull injuries or dislocations of anatomic structures, as well as for the lack of involvement of the extra- and intracranial sections of the vertebral arteries.

Disclosure: Nothing to disclose

P1116

Etiological variability after recurrent stroke

C.A. Calle de Miguel[1], P. Martínez Sánchez[1], E.M. Alba Suarez[1], J. Díaz De Terán[1], J. Rodríguez Pardo de Donlebún[1], J. Pérez Lucas[1], I. Illán Gala[1], B.E. Sanz Cuesta[1], B. Fuentes[1], E. Díez-Tejedor[2]
[1]Hospital Universitario La Paz, Neurology, Madrid, Spain, [2]Hospital Universitario la Paz, Neurology department and Stroke centerdepartment and Stroke center, Madrid, Spain

Background and aims: To analyze the etiology of recurrent ischemic stroke and to investigate in which cases a different cause was detected in the second event.

Methods:: Observational study of patients with ischemic stroke (2010-2014). Variables: Baseline/clinical data, prior cerebral infarction (CI) or transient ischemic attack (TIA). Etiologies of current and previous stroke/TIA and their concordance were recorded.

Results: A total of 1197 patients were included, 57.1% were male, mean age 70.5 years. 18.5% (222) had a prior ischemic stroke (CI 58.1%, TIA 34.2% and TIA+CI 7.7%). The cause of the previous stroke was: undetermined / unreported (53.2%), cardioembolic (17.1%), lacunar (13.3%), atherothrombotic (9.2%) and unusual (3.2%). The concordance between past and present etiology was analyzed, being the most consistent cardioembolic (94.7%), followed by atherothrombotic (74.1%) and unusual (62.5%), with low agreement in the lacunar (30%) and undetermined (39.8%) ($P < 0.0001$). The most frequent cause of recurrence in lacunar and undetermined / unreported stroke was the cardioembolic cause (37.5% and 40%, respectively). In 39.8% of prior strokes of undetermined etiology, a current cause was not identified. The mean time to recurrence was higher in those who changed etiology respect to those who maintained the previous (73.1 vs. 46.3 months, $P=0.003$).

Conclusion: The etiologic subtype that most frequently recurs with the same etiology is cardioembolic stroke. Current cardioembolic cause is more frequent in patients with prior lacunar or undetermined/unreported strokes. In up to one third of patients with stroke of undetermined / unreported cause, no etiology is found after recurrence.

Disclosure: Nothing to disclose

P1117

Multiple simultaneous spontaneous intra-cerebral hemorrhages: long-term outcome.

Y. Chen, D. Leys, H. Henon, S. Bombois, F. Pasquier, C. Cordonnier

Univ. Lille Nord de France, UDSL, CHU Lille, U 1171, Lille, France

Background and aims: In hospital databases, multiple simultaneous spontaneous intracerebral hemorrhages (ICH-m) account for 0.7% to 5.6% of all ICH. Their long-term outcome has never been systematically and prospectively investigated. We aimed at identifying the long-term outcome of patients with ICH-m.

Methods: We prospectively recruited consecutive adults with ICH-m, and followed them up for at least 4.5 years. We classified patients into 3 groups: (i) definite or probable cerebral amyloid angiopathy (CAA); (ii) deep perforating vasculopathy; and (iii) unknown causes.

Results: Of 562 consecutive patients with intracerebral hemorrhages, 32 had multiple simultaneous spontaneous intracerebral hemorrhages (5.7%): 8 (25%) with probable cerebral amyloid angiopathy, 5 (16%) with deep perforating vasculopathy, and 19 (59%) with intracerebral hemorrhages of unknown cause. At the last visit (cumulative follow-up of 39.5 person-year), 27 patients (84%) had died, and 3 of the 5 survivors were independent. Late onset seizures, recurrent intracerebral hemorrhages (symptomatic or not), and new brain microbleeds were mainly found in patients with probable cerebral amyloid angiopathy.

Conclusion: ICH-m is a rare but extremely severe expression of ICH. Survivors with CAA are more likely to develop late seizures and new hemorrhagic lesions. Because of low survival rates, large multicentre cohort studies are needed for a better understanding of this rare condition.

Disclosure: Nothing to disclose

Headache and pain 1

P1118

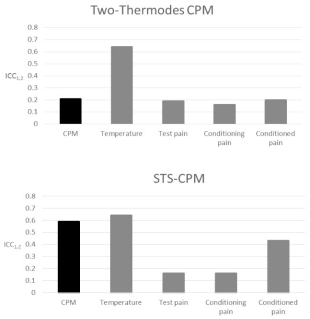
CPM test-retest reliability of two heat pain protocols

Y. Granovsky[1], A. Miller[2], T. Alon[1], O. Goldstein[2], E. Sprecher[1], D. Yarnitsky[1]
[1]Rambam Health Care Campus, Haifa, Israel, [2]Rambam healthcare campus, Haifa, Israel

Background and aims: The assessment of pain inhibitory mechanisms using conditioned pain modulation (CPM) is relevant clinically in prediction of pain and of analgesic efficacy. The practical transformation of the CPM paradigm into a clinical tool, however, depends on its reliability along time. In this paper we present reliability data for two thermal heat CPM protocols specifically developed with the intention of improving reliability of the CPM assessment.

Methods: A cohort of young healthy subjects (total N=30, 15 females) participated in a dual-session study consisted of two CPM protocols : (1) Two-Thermodes, one for conditioning stimuli, and a second for test-stimuli, in a classical parallel CPM design- introducing test stimulus first, and then the conditioning and repeated test stimuli in parallel, and (2) Single test-stimulus (STS) protocol with a single administration of a contact heat test-stimulus, partially overlapped in time by a remote shorter contact heat as conditioning stimulus. Reliability was assessed using intraclass correlation (ICC) analysis.

Results: Test-retest reliability was assessed within 3-7 days. The STS-CPM had superior reliability (ICC2,1=0.59) over the Two-Thermodes (ICC2,1=0.21) protocol. Conditioned test-stimulus pain scores were of fair (ICC2,1=0.43) reliability for the STS, but not for the Two-Thermodes protocol (ICC2,1=0.20).



ICC values for main CPM-related variables

Conclusion: The newly developed STS-CPM paradigm has superior reliability over a parallel CPM protocol, and should be further investigated for its clinical relevance.

Disclosure: No author has potential conflict of interests. Dr. Yelena Granovsky is a paid scientific consultant of Medoc Ltd. This study was funded by a grant from the Office of the Technion's Vice President for Research.

P1119

Effect of body mass index on CS Fopening pressure

S. Al-Othman[1], H. Mistry[1], R. Atkinson[1], R. Mohanraj[2]
[1]Salford Royal Hospital NHS foundation trust, Neurology, Salford, United Kingdom, [2]Salford, United Kingdom

Background and aims: Opening pressure of cerebrospinal fluid (CSF), measured by lumbar puncture (LP) may be influenced by patients' body habitus. Abnormalities of CSF pressure such as Idiopathic Intracranial Hypertension are thought to be more common in patients with high body mass index (BMI). It is important to ascertain normal values of CSF opening pressure for patients in each BMI category. We analysed the relationship between BMI and CSF opening pressure in 279 patients undergoing LP to ascertain normal values for patients of varying BMI.

Methods: Data on height, weight and CSF opening pressures of patients who underwent elective LP were analysed. Patients with known or suspected intracranial hyper- or hypotension were excluded, as were those whose eventual diagnosis was one known to affect CSF opening pressure. Data on 279 patients were included.

Results: Obese patients (BMIs >30, n=90) had a median CSF opening pressure of 23cm of CSF (range 10-36), which was significantly higher than that for overweight patients (BMI 25-30, n=84); 16.75cm of CSF (8-31) and for those with normal or low BMI (<25, n=105); 14cm of CSF (range 7.5-31). There was a statistically significant correlation between CSF opening pressure and BMI (Pearson's product-moment correlation: 0.628). We used linear regression to show a significant relationship between BMI and CSF opening pressure: coefficient 0.611 ($p<0.001$, 95% CI- 0.521 - 0.700).

Conclusion: Normal values of CSF opening pressure are significantly higher in obese and overweight patients. There is a linear relationship between BMI and CSF opening pressure.

Disclosure: Nothing to disclose

P1120

Reliability and repeatability of testing Visual Evoked Potentials in migraine

A. Ambrosini[1], G. Coppola[2], E. Iezzi[1], F. Pierelli[3], J. Schoenen[4]

[1]IRCCS Neuromed, Pozzilli (Isernia), Italy, [2]IRCCS G.B. Bietti Foundation, Rome, Italy, [3]"Sapienza" University Polo Pontino, Latina, Italy, [4]CHR CItadelle - University of Liège, Liege, Belgium

Background: In most studies migraineurs have an interictal habituation deficit of visual evoked potentials (VEP). This, however, was not confirmed in some studies, which was attributed to low reliability and repeatability.

Aim: To test in healthy volunteers (HV) and episodic migraineurs (EM): 1) reliability of VEP habituation measures by comparing blinded and non-blinded analyses; 2) VEP repeatability by evaluating two recordings separated in time.

Methods: To test VEP reliability, pattern-reversal VEP were recorded in 22 HV and 44 EM. Two researchers, one of which was totally blinded to subjects and diagnosis, independently analysed single trials and calculated habituation percentages. To test VEP repeatability, two VEP recordings, separated by a time interval ranging from 7 to 120 days, were performed in 12 HV and 9 EM.

Results: In both the blinded and the non-blinded analysis VEP habituation was normal in HV, but deficient in EM. The difference between HV and EM was significant for both procedures ($p=0.038$ and $p<0.001$) and data were significantly correlated (overall $r=0.780$, $p<0.0000001$). When recordings were repeated twice, habituation values and differences between study groups were similar in the two recordings, and intraindividual data for both recordings were significantly correlated (overall $r=0.700$, $p=0.0004$).

Conclusion: We confirm that VEP habituation is interictally deficient in episodic migraineurs also when analyses are blinded and recordings repeated. Low reliability or repeatibility can thus not explain the discrepant results found by others.

Disclosure: Nothing to disclose

P1121

Successful treatment with jugular stenting of exercise-induced intracranial hypertension mimicking status migrainosus

P. Michel[1], A. Angelillo-Scherrer[2], P. Maeder[3], S. Binaghi[3], I. Meyer[1], P. Correia[1]

[1]CHUV, Lausanne, Neurology , Lausanne, Switzerland, [2]Bern University Hospital, University of Bern, Department of Hematology and Central Hematology Laboratory, Berne, Switzerland, [3]CHUV, Lausanne, Department of Diagnostic and Interventional Radiology, Lausanne, Switzerland

Background:cerebri mention venous outflow as a potential cause. We describe a patient developing episodic exercise-induced intracranial hypertension manifesting as status migrainosus years after internal jugular vein (JV) obstruction.

Methods: The clinical and radiological findings are described and the probable pathogenesis and treatment discussed.

Results: An 18-year-old non-obese male had a motorcycle accident resulting in left brachial plexus avulsion and asymptomatic left vertebral artery dissection. Seven years later, he had prolonged headache episodes, precipitated by strenuous sporting activities, fulfilling criteria for status migrainosus. Head CT and fundoscopy were normal. Lumbar punctures showed severe intracranial hypertension (IH >50 cmH2O) during but not after attacks with complete headache relief within 20 minutes. Oral acetazolamide was unsuccessful. CT venography during an episode showed compression of transverse sinuses and cervical MR venogram confirmed chronic (likely posttraumatic) subocclusion of left JV and stenosis of right JV, most likely from central venous catheterization. Because of worsening episodes including aphasia, hemiparesis and Cushing reflex, right JV stenting was performed. Several in-stent thromboses occurred despite antithrombotic treatment, causing additional episodes of IH.These resolved under quadruple antithrombotic therapy which was tapered over 3 years, and the patient became asymptomatic under aspirin only.

Conclusion: Episodic severe IH in our patient probably occurred because of exercise-induced pressure elevation in the vena cava, causing decompensation of a borderline venous return from bilateral posttraumatic JV obstruction. Pathophysiology-based treatment with JV stenting was initially complicated by recurrent in-stent thromboses,but resolved under quadruple antithrombotic treatment which was tapered.

Disclosure: Nothing to disclose

P1122

Clinical picture of Epicrania Fugax: a prospective series of 55 cases

M. de Lera Alfonso[1], R. Marina[2], M. Irene[2], H. Avellón[3], J. Baron Sanchez[4], R. Moreno[5], M. Pedraza[4], L. López[6], A.L. Guerrero[4]

[1]Valladolid, Spain, [2]Hospital Clínico Universitario de Valladolid, Neurology, Valladolid, Spain, [3]hospital Clínico Universitario de Valladolid, Valladolid, Spain, [4]Valladolid Hospital, Neurology, Valladolid, Spain, [5]Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [6]hospital clínico Universitario de Valladolid, Neurology, Salamanca, Spain

Background and aims: Epicrania fugax (EF) has been included in the research appendix of International Classification of Headache Disorders, III edition. It is defined by brief, recurrent pain attacks, moving forwards or backwards across the surface of one hemicranium. We aim to analyze clinical characteristics of a series of patients attended in an outpatient headache office in a tertiary hospital.

Methods: We considered consecutive patients with EF from March 2008 to January 2015. We prospectively assessed spatial and temporal features of paroxysms, quality and intensity of pain, and presence of accompaniments, triggers or interictal pain.

Results: 55 patients (40 females, 15 males) out of 3357 attended during inclusion period (1.6%) were diagnosed with EF. Mean age at onset 42.8 ± 17.2 years (range: 18-84). In 39 cases (70.9%) forward radiation, in 15 (27.3%) backward, whilst in 1 (1.8%) paroxysms described both trajectories. In forward EF, pain stemmed in occipital (29, 72.5%) or parietal scalp (9, 22.5%) and ended at eye (22, 55%) or forehead (12, 30%). When backward EF, pain radiated from frontal region (7, 43.7%) or eye (5, 31.2%) to occipital (9, 56.2%) or parietal scalp (4, 25%). Pain quality was mainly described as electric (50, 90.9%), and intensity rated as 6.8±1.8 (3-10). Complete sequence was very brief (usually <10 seconds). 8 (14.5%) patients identified triggers, commonly neck movements and 19 (34.5%) associated autonomic features, mainly lacrimation.

Conclusion: This new series reinforces the proposal of EF as a new headache syndrome. Characteristics of forward and backward EF were comparable in our series.

Disclosure: Nothing to disclose

P1123

Different type of headache syndromes in patients with idiopathic intracranial hypertension (IIH)

P. Gelener[1], S. Ucler[2], Ö. Coskun[3], L.E. Iinan[4]

[1]nicosia state hospital, neurology, Nicosia, Cyprus, [2]Okmeydanı Training and Research Hospital, neurology, istanbul, Turkey, [3]gazi university hospital, neurology, Ankara, Turkey, [4]ankara traning and research hospital, neurology, Ankara, Turkey

Background and aims: Idiopathic Intracranial Hypertension (IIH) is a neurologic syndrome characterized by elevated intracranial pressure in the absence of intracerebral abnormalities or hydrocephalus. The most frequent symptom is headache. We aimed to investigate different types of headache sydromes that may accompany the disease in 57 patients.

Methods: Total of 57 patients who were diagnosed with IIH according to modified Dandy Criteria was included in the study. Detailed headache history was questioned. The patients were also asked to fill in detailed headache forms specially prepared to question different headache types.

Results: In the 51.8% of the patients included in the study, we observed different headache sydromes accompanying or associating with IIH. 33.9% of the patients had stabbing headache whereas 12.5% had migraine like-headache, 7.1% had tension type headache and 5.4% had hemicrania continua.

Conclusion: Migraine, tension type and medication overuse headaches are known to accompany IIH since long time. In our patient group, distinctively from the literature, stabbing headache was more common.

Disclosure: Nothing to disclose

P1124

Reduced baroreflex sensitivity in cluster headache patients

M. Barloese[1], J. Mehlsen[2], L. Brinth[2], H.I.S. Lundberg[3], P.J. Jennum[4], R. Jensen[5]

[1]Copenhagen, [2]Frederiksberg Hospital, Clinical Physiology and Nuclear Medicine, Frederiksberg, [3]Glostrup Hospital, Diagnostic Department, clinical physiology and nuclear medicine section, Frederiksberg, [4]Glostrup - Copenhagen, [5]University of Copenhagen, Neurology, Copenhagen, Denmark

Background and aims: Important elements of cluster headache (CH) pathophysiology may be seated in the posterior hypothalamus. Cranial autonomic features are inherent, but involvement of systemic autonomic control is still debated. The aim of this investigation was to characterize autonomic function by investigating baroreflex sensitivity (BRS) in CH patients.

Methods: 26 CH patients (in bout) and an equal number of age-, sex- and BMI-matched controls underwent head-up tilt table test. BRS was determined by the sequence method.

Results: Compared to controls, patients exhibited a blunted shortening of RR intervals to falls in systolic blood pressure (SBP) (14.3 vs. 22.3 ms/mmHg, $P<0.05$) in the supine position. Also, compared to controls, BRS was lower in patients having suffered an attack within the past 12 h (12.5 vs. 22.3 ms/mmHg, $P<0.01$), opposed to those patients who had not (16.0 ms/mmHg, $P>0.05$). In the tilted position the drop in SBP at the carotid sinuses was higher in patients who had recently suffered an attack. Despite this they exhibited a less marked shortening of RR intervals when compared to patients who had been attack free for longer.

Conclusion: CH patients exhibit a blunting of BRS which may be affected by the attacks themselves. The fast RR interval fluctuations used in this method reflects cardiovagal responses, thus the blunted responses are suggestive of dysfunction in the parasympathetic division of the autonomic nervous system or in the central relay of impulses from the baroreceptors.

Disclosure: Nothing to disclose

Infection and AIDS 1

P1125

Expression of CCR5 on T-cells in progressive multifocal leukoencephalopathy-associated immune reconstitution inflammatory syndrome: Rationale for the use of Maraviroc

G. Martin-Blondel[1], J. Bauer[2], B. Pignolet[3], E. Uro-Coste[4], D. Biotti[5], D. Averseng-Peaureaux[5], N. Fabre[5], H. Dumas[6], F. Bonneville[7], H. Lassmann[8], B. Marchou[1], R. Liblau[9], D. Brassat[10]

[1]Department of infectious diseases, Toulouse University Hospital, France, Toulouse, France, [2]Center for brain research, Medical University of Vienna, Austria, Vienna, Austria, [3]inserm, Toulouse, France, [4]Department of pathology, Toulouse University Hospital, France, Toulouse, France, [5]Department of neurology, Toulouse University Hospital, France, Toulouse, France, [6]Department of neuroradiology, Toulouse University Hospital, France, Toulouse, France, [7]CHU Purpan, Neuroradiologie, Toulouse, France, [8]Center for Brain Research, Medical University of Vienna, Department of Neuroimmunology, Vienna, Austria, [9]Toulouse, France, [10]Hopital PPR - CHU Purpan, Neurology, Toulouse, France

Background and aims: Therapeutic strategies that modulate the deleterious immune response underlying progressive multifocal leukoencephalopathy-associated immune reconstitution inflammatory syndrome (PML-IRIS) are warranted. Maraviroc, an antagonist of the CCR5 chemokine receptor, has been suggested to be beneficial in preventing or treating PML-IRIS. We investigated whether the molecular target of maraviroc is expressed on T-cells circulating and infiltrating PML-IRIS lesions.

Methods: We analyzed brain lesions of 7 patients with inflammatory forms of PML, 2 with iatrogenic immunosuppression (1 Natalizumab-treated MS patient and 1 patient treated for chronic lymphocytic leukemia) and 5 HIV-infected patients. We are furthermore analyzing CCR5 expression by blood circulating T-cells in nine natalizumab-treated patients at the onset of PML and of PML-IRIS.

Results: In all cases, histological analysis revealed demyelinating lesions and the presence of JC virus-infected cells, confirming PML. CD8+ T-cells dominate in the inflammatory infiltrates. Confocal fluorescence staining showed that 93.7±2.2% of the perivascular and parenchymal CD8+ T-cells express CCR5. CD4+ T-cells and macrophagic/microglial cells also expressed CCR5, albeit at weaker levels than CD8+ T-cells. The two non HIV-infected patients were treated with maraviroc to prevent or treat PML-IRIS, with a favorable outcome. Analysis of CCR5 expression by circulating CD8+ T-cells is ongoing.

Conclusion: Since the CCR5/CCL5 axis is implicated in T-cell activation and in leukocyte trafficking to the brain, our results suggest that CCR5 antagonists can mitigate the deleterious immune response underlying PML-IRIS, deserving further studies.

Disclosure: Nothing to disclose

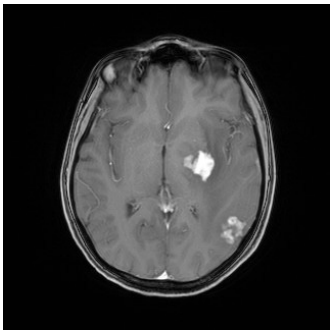
P1126

Disseminated intracerebral tuberculosis infection with mycobacterium bovis in an immunocompetent young female

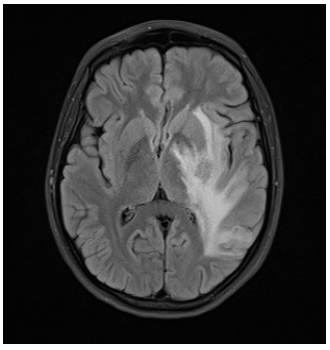
T. Bruening[1], H. Berling[2], B. Hoepfl[3], A. Vanegas-Ramirez[4], R. Ritzel[5]

[1]Bundeswehrkrankenhaus, Neurology, Hamburg, Germany, [2]Bundeswehrkrankenhaus, Internal Medicine, Hamburg, Germany, [3]Bundeswehrkrankenhaus, Neurosurgery, Hamburg, Germany, [4]Bundeswehrkrankenhaus, Dermatology, Hamburg, Germany, [5]Bundeswehrkrankenhaus, Radiology, Hamburg, Germany

Case Report: We report the case of a 23-year-old women from Morocco with disseminated intracerebral tuberculosis. In November 2013 our pregnant patient suffered from an epileptic seizure with aphasia, myoclonia of head and right arm and secondary generalization for the first time. Further seizures occurred during delivery and in following months, EEG was performed and anticonvulsive medication with valproic acid started, she suffered from ongoing seizures. Except repeated gynaecological infections in 2013 there were no signs of immune deficiency. Neurological status and physical examination were without pathological findings disregarding language barrier. Laboratory, faecal diagnostic, cerebrospinal fluid and further examinations remained without trend-setting findings. Magnetic resonance imaging of brain revealed multifocal lesions with blood-brain barrier disorder and distinct perifocal edema. Acid-proof rods could not be proved. We discussed cerebral metastasis, sarcoidosis and tuberculosis. Cerebral biopsy verified inflammatory granulomatous process with epithelioid cellular histiocytes and Langhans giant cells. We started medical treatment with a combination of ethambutol, rifampicin, isoniazid and pyrazinamid, cortison and vitamin B6. Biopsy culture result revealed Mycobacterium tuberculosis complex, subspecies M. bovis, as far as we know a rare finding. In follow up examination after 6 and 12 weeks of therapy patient presented with stable disease with mild remission of MRI findings, we replaced pyrazinamid by fluorochinolone due to agent resistence. What did we learn? It is tremendous important to force diagnostic steps in order to find the diagnosis. The key to the diagnosis in our case and gold standard finally was the culture from the cerebral biopsy.



MRI T1 contrast medium



MRI T2 FLAIR dark fluid

Disclosure: Nothing to disclose

P1127

The prevalence of neuropsychiatric symptoms in Lyme borreliosis patients

S. Cihelková
Charles University Prague, Department of Infectious Diseases of 1st Medical Faculty, Prague, Czech Republic

Background and aims: Although a neuropsychiatric symptom in Lyme borreliosis (LB) is frequent and may be a tool for monitoring and diagnosis of neuroborreliosis, the data of prevalence are poor, especially about such symptoms as somatization, interpersonal irritability and fatique.. The aim of this study was to assess the frequency of each symptom common in LB or inflammatory diseases, not only psychiatric illnesses and their relationship.

Methods: The 40 consecutive patients with all stages of LB, diagnosed at Department of infectious Diseases of 1nd Medical Faculty of Charles University in Prague and 30 healthy controls were included to the study. All patients were examined by self-evaluated scales for mood, fatigue and personality - BDI II, BAI II, SCL-90, Fatigue MS scale, EOD II.A or B, Hamilton depression and anxiety scales.

Results: The most common symptoms were fatigue and abnormal or pathological interpersonal irritability and somatization (according SCL score); these symptoms seem to be associated with depression (45%) and anxiety (80%) as symptoms, not as psychiatric disorders. Interestingly, the scare from LB is associated with these symptoms in 87%. It is important to take enough time to inform patients.

Conclusion: The study confirmed a results of previous study – the symptoms depresssion and anxiety prevalence. Furthermore, the somatization, interpersonal irritability and fatique are also important for medical care and next investigation.

Disclosure: Nothing to disclose

P1128

Herpes Human Virus-7 (HHV-7) myelitis in an HIV-infected patient successfully treated with foscarnet

A. Escobar-Villalba[1], I. Corral Corral[1], P. Pérez Torre[1], J. Buisan[1], M. Rodriguez[2], J.C. Galan[2], P. Agüero Rabes[1], E. Viedma-Guiard[2], M.M. Kawiorski[1], C. Estevez-Fraga[2]
[1]*Hospital Ramón y Cajal, Neurology, Madrid, Spain,*
[2]*Hospital Ramon y Cajal, Madrid, Spain*

Background and aims: HHV7 reactivation has been occasionally reported as a cause of encephalitis or myelitis in transplant recipients, but to our knowledge it has never been associated with neurological disease in HIV-infected patients. We report a case of acute myelitis in an HIV-infected patient, with sustained HHV-7 DNA amplification in cerebrospinal fluid (CSF) and a favourable response to foscarnet.

Case Report: A 40-year-old man with HIV infection known for 8 years, was admitted with asymmetric hypoesthesia in legs and paraparesis which progressed along 30 days. He was receiving treatment with efavirenz, tenofovir, emtricitabine (atripla) and his CD4 count was 580/mm^3 and HIV viral load was undetectable. Magnetic resonance imaging showed a focal central hyperintensity on T2 and STIR sequences, on the thoracic spinal cord, with slight enhancement after intravenous gadolinium. CSF contained 4 lymphocytes and 19.98mg/dl proteins. All microbiological studies were negative except for HHV-7 DNA amplification in CSF. With a diagnosis of idiopathic transverse myelitis, treatment with high-dose intravenous methylprednisolone was initiated. However, paraparesis continued worsening, and a second CSF obtained twelve days after the first one resulted again in HHV-7 amplification.

Results: The patient was treated with a 2 week course of foscarnet, and a rapid neurological improvement was noted. After treatment PCR for HHV-7 in CSF was negative. Neurological exam was normal one month after treatment initiation.

Conclusion: HHV-7 reactivation may cause neurological disease in patients with HIV infection. Foscarnet is an effective treatment in HHV-7 associated myelitis.

Disclosure: Nothing to disclose

P1129

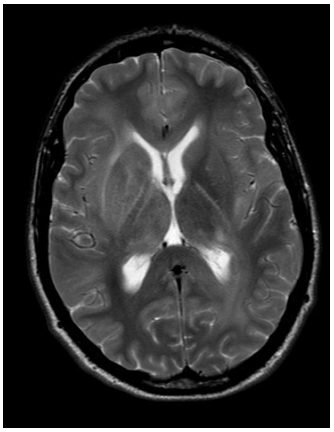
Unusual neurological immune reconstitution syndrome in HIV

P. Holmes[1], R. Kulasegaram[2]
[1]Guy's and St Thomas' Hospitals, Neurology, London, United Kingdom, [2]Guys and St Thomas' Hospitals, HIV and GU Medicine, London, United Kingdom

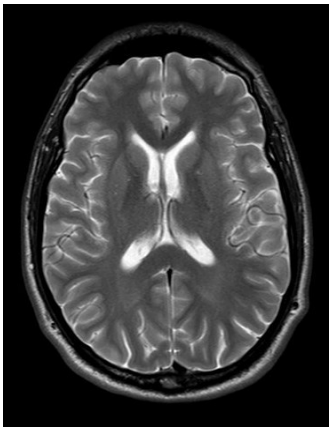
Background and aims: When started on anti-retroviral therapy (ARV), and associated with a decline in plasma HIV-RNA and a rise in CD4 count, a subset of patients with HIV infection deteriorate clinically due to an inflammatory process termed immune reconstitution inflammatory syndrome (IRIS). This condition results from the restoration of the immune system that upon activation can be detrimental to the host. Among the various clinical manifestations, central nervous system involvement is associated with greater morbidity and mortality. There are two versions, a paradoxical one occurring when an opportunistic infection, responding to treatment before ARV therapy, deteriorates after initiating ARVs and an unmasking variant where a disease that was cryptic prior to starting ARVs, presents after starting ARVs with florid, inflammatory symptoms.

Methods: We present 5 cases of an unusual neurological IRIS manifestation that is rare and highlights the importance of the clinical history, neuroimaging and adherence to ARV. The condition occurs as a result of variable compliance with ARV and appears as an HIV encephalitic IRIS manifestation due to intermittent documented high CSF viraemia. Pathogen-related factors and features of the host immune response determine the predisposition to neuro-IRIS. MR imaging is unique as shown.

Results: Patients presented with progressive severe multifocal neurological symtpoms and signs and as a result of severe inflammation and swellling developed decreasing levels of consciousness prompting ITU admission and use of high dose steroids.



T2-weighted MRI showing diffuse cortical swelling and subcortical grey and white matter high signal



T2-weighted MRI showing near complete resolution of the changes after steroids and ARV

Conclusion: The condition appears to be that of a rebound HIV viral encephalitis. Imaging features are dramatic but show near complete resolution after steroids and ARV compliance.

Disclosure: Nothing to disclose

P1130

The spectrum of viral CNS infections in Southern Germany - demographic, clinical and laboratory findings

M. Kaminski, V. Grummel, A. Berthele, B. Hemmer
Klinikum rechts der Isar, Technische Universität München, Neurology, Munich, Germany

Background and aims: Viral infections of the central nervous system (CNS) are frequently observed in Germany. However, no study has systematically addressed spectrum of viruses, frequency and seasonal distribution causing meningitis and meningoencephalitis/encephalitis. Moreover, the impact of specific viral-CNS-infections on clinical and laboratory findings is poorly defined.

Methods: Data of 176 adult patients diagnosed from 01/2007-06/2014 with viral meningitis and meningoencephalitis/encephalitis at our hospital was collected by chart review. Analyzed demographic data included age, sex and month-of-infection. We studied frequency of each detectable virus-group and reviewed accordingly laboratory-parameters in cerebrospinal fluid (CSF) and serum. In addition, we performed column statistics of demographic and clinical data and compared laboratory-data of virus-groups.

Results: In our cohort, viral meningitis was caused in 36% by enterovirus (EV), 18% by herpes-simplex-virus (HSV), 13% by varicella-zoster-virus (VZV) and 11% by early-tick-borne-encephalitis (TBE). Viral meningoencephalitis/encephalitis was caused in 16% by HSV, 11% by VZV and 2% by TBE. Mean age was 45y at diagnosis. Incidence of VZV and EV caused infections was highest during summer, HSV infections showed no seasonal preference. VZV meningitis had a bimodal distribution with a peak below 30y and above 70y. CSF-cell-count, CSF-lactate, albumin-quotient and serum-CRP were highest in HSV and lowest in EV mediated CNS infections.

Conclusion: PCR for HSV, VZV and EV in CSF and TBE serology determine the causative virus in over 60% of tested patients. EV-infections were most common and show lower inflammatory changes in CSF and serum. By contrast HSV-infections, not showing a seasonal preference, have a higher inflammatory response in CSF and serum.

Disclosure: Nothing to disclose

P1131

Detection of human herpesvirus 7 DNA in CSF in adult patients with neurological disorders

S. Sainz de la Maza[1], M.J. López-Martínez[1], M.M. Kawiorski[1], A. De Felipe Mimbrera[1], A. Alonso-Canovas[1], M.J. Rodríguez[2], J.C. Galán[2], I. Corral[1]
[1]Hospital Universitario Ramon y Cajal, Neurology, Madrid, Spain, [2]Hospital Universitario Ramón y Cajal, Microbiology, Madrid, Spain

Background and aims: Human herpesvirus type 7 (HHV-7) possess neurotropism. Neurological manifestations associated with HHV-7 have been described in primary infection in children, and very occasionaly in viral reactivation in immunocompromised patients. However, prevalence of HHV-7 DNA amplification in CSF from general population is not known, and the role of HHV-7 reactivation as a cause in central nervous system (CNS) diseases in immunocompetent adults has not yet been defined.

Methods: Retrospective analysis of clinical and microbiological features of adults with neurological symptoms who underwent lumbar puncture, and had a multiplex polymerase chain reaction (PCR) for herpesviruses and enteroviruses performed in CSF.

Results: A total of 251 subjects (121 female) were included. Mean age 55 years [15-89]. HHV-7 DNA was detected in 4/169 CSF samples from patients with diagnosis of non-infectious neurological disorders (Specificity 0.976), and in 1/36 from patients with microbiologically confirmed CNS infections (Specificity 0.972). HHV-7 DNA was also detected in CSF samples from 6 patients with probable CNS infections (compatible clinical syndrome and CSF changes) in the absence of causative agent: 4 meningitis, 1 encephalitis, 1 myelitis. The latter two, with severe CNS infections, were treated with Foscarnet, achieving improvement of symptoms and disappearance of HHV-7 DNA in follow-up CSF.

Conclusion: Detection of HHV-7 DNA in CSF as a false positive result or asymptomatic reactivation in patients with neurological conditions is uncommon. HHV-7 reactivation may cause CNS disease in immunocompetent adults. Foscarnet seems to be an adequate treatment for HHV-7 CNS disease

Disclosure: Nothing to disclose

P1132

Neurological manifestations among patients with HIV – active tuberculosis coinfection, Sudan 2014

M. Taha[1], A. M. Hussein[2], M. Dafaallah[3], M. Alfaki[1], M.A. Abdelrahim[4]

[1]*daoud research group, khartoum, Sudan,* [2]*Faculty of medicine, University of Khartoum, Department of Neurology, khartoum, Sudan,* [3]*daoud research group,* [4]*Khartoum, Sudan*

Introduction: At least one-third of the 35.3 million people living with HIV worldwide are infected with latent tuberculosis. Tuberculosis is the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment. There were an estimated 1.1 million HIV positive new TB cases globally in 2012. Around 75% of these people live in sub-Saharan Africa (WHO HIV-Associated TB Facts 2013). Despite its great burden, neurological manifestations have not been described yet in patients with HIV-active tuberculosis, although tuberculosis and HIV have synergistic influence on immunity system which may contribute to change in prevalence or severity of CNS involvement in patients with HIV-active TB coinfection.

Objectives: To study neurological manifestations in patients with HIV-active tuberculosis

Methods: A case series study of 58 consecutive patients with laboratory confirmed HIV- active tuberculosis coinfection attending tertiary hospital for tuberculosis treatment was conducted. Data about neurological symptoms and signs – conducted by a neurologist- were collected from each patient. Patients approval was obtained.

Results: 24% of 58 patients were found to have neurological manifestations in clinical assessment. This table demonstrates the neurological manifestations and their frequency.

Neurological Diagnosis

	Frequency	Percent
normal	44	75.9
AIDS Dementia	3	5.2
Meningitis	2	3.4
Grand mal epilepsy	2	3.4
cerebellar ataxia	1	1.7
GBS	1	1.7
peripheral neuropathy	1	1.7
proximal weakness	1	1.7
spastic quadriplegia	1	1.7
stroke	1	1.7
transverse myelitis	1	1.7
Total	58	100.0

Conclusion: the frequency of neurological manifestations among patients with HIV-active TB coinfection was found to be higher compared to that of patients with HIV only; 20% (Wadia et al, 2001).

Disclosure: Nothing to disclose

Motor neurone diseases 1

P1133

Longitudinal assessment of frontal cognitive impairment in patients with motor neuron disease

P.M. Ferraro[1], F. Agosta[1], E. Canu[1], E.G. Spinelli[1], N. Riva[2], M. Copetti[3], G. Comi[4], M. Filippi[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Hospital, Milan, Italy, [3]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy

Background and aims: To test the progression of frontal cognitive impairment in patients with motor neuron disease (MND).

Methods: 28 non-demented patients with recently diagnosed sporadic MND were followed prospectively with clinical and neuropsychological evaluation every 3 and 6 months respectively, for a maximum follow-up of 24 months. Cognitive assessment was performed using the MMSE, verbal fluency tests, and the Test of Attentional Performance (TAP). The TAP, which is administered through an automated computerized system, permits to investigate the whole spectrum of frontal involvement in ALS, reducing verbal and/or physical disability. Longitudinal linear models were used to assess clinical and cognitive variable changes over time and the relationship between baseline clinical features and cognitive deterioration.

Results: During follow-up, MND patients experienced a progressive worsening of motor disability, with a statistically significant decrease over time of the ALSFRSR scale score ($p<0.001$), total MRC ($p<0.001$) and ALS severity scale ($p<0.001$), and increase of the upper motor neuron score ($p<0.001$). MND patients also showed a significant deterioration of the global cognition ($p=0.04$), semantic fluency ($p=0.03$), and several frontal measures (p ranging from <0.001 to 0.04). The TAP showed that sustained attention, behavioural control and interference tendency significantly decreased over time. The progressive cognitive decline was independent of baseline motor clinical characteristics.

Conclusion: Longitudinal analyses using computerize-based, sensitive executive measures revealed a progressive cognitive decline which appeared relatively early in the course of MND.

Disclosure: Italian Ministry of Health (#RF-2010-2313220).

P1134

MRI biomarkers in sporadic amyotrophic lateral sclerosis: a follow-up study.

G. Grolez[1], C. MOREAU[1], V. Danel Brunaud[1], P. Jissendi[2], R. Lopes[2], A. Monnet[2], J. Hodel[2], P. Besson[2], T. Hamel[2], C. Delmaire[2], L. Defebvre[1], D. Devos[3]
[1]Department of Movement Disorders, Lille Nord de France University, CHU Lille, Lille, France, [2]Department of Neuroradiology, Lille Nord de France University, CHU Lille, Lille, France, [3]Lille Nord de France University, CHU Lille, Lille, France, Department of Movement Disorders; INSERM U1171; Department of Movement Disorders, Lille, France

Background and aims: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, which mainly affects motor neurons in cerebral cortex and spinal cord. Recently, regional iron overload has been demonstrated in the medulla of SOD mice model. Iron (measured by the R2* sequence of the magnetic resonance imaging, MRI) can further enhances free radicals formation by the mitochondrial dysfunction. The aim of our study was to assess the most sensitive MRI biomarkers of ALS with longitudinal analysis.

Methods: 29 ALS patients and 21 healthy volunteers were included. 29 patients had a baseline analysis and 19 patients had a second MRI examination after 4 months. The R2*, volumetry, spectroscopy and diffusion tensor imaging (DTI) sequences were analyzed with 3 Teslas brain and medulla MRI.

Results: At baseline, diffuse brain atrophy and higher R2*/volume ratios were observed in patients as compared with controls with predominance in motor cortex and bulbar area. DTI and spectroscopy results correlated with volume assessment, with increased mean diffusivity and decreased N-acetyl aspartate/creatine ratios. The follow up showed a significant higher R2* value and atrophy in cervical spinal cord.

Conclusion: To date, the most sensitive parameter to diagnose ALS remains brain atrophy. The most sensitive parameters of disease progression were the R2* value and the volume of cervical spinal cord. The latter could be very promising as surrogate biomarkers with the resolution of technical difficulties.

Disclosure: The authors have no financial disclosures to make or potential conflicts of interest to report in relation to this investigator-driven study. The study was funded by the French Ministery of Health: PHRC (Projet Hospitalier Recherche Clinique) grants : Protocol ID: 2008-006842-25.

P1135

Auditory mismatch negativity (MMN) as a marker for motor neuron disease

P.M. Iyer[1], B. Michels[2], B. Nasseroleslami[3], E.C. Lalor[4], O. Hardiman[3]

[1]Dublin, Ireland, [2] Trinity College, School of Engineering, Dublin [2], Ireland, [3] Trinity College, Trinity Biomedical Science Institute,, Dublin [2], Ireland, [4], Trinity College, School of Engineering, Dublin [2], Ireland

Background and aims: There is an urgent need to develop biomarkers in Amyotrophic Lateral Sclerosis (ALS) as it is heterogeneous in phenotype, genotype and disease progression and prognosis. We studied whether auditory mismatch negativity (MMN) could be used as a marker in ALS, using spectral EEG. MMN is the difference between EEG responses when a deviant tone is presented unexpectedly while listening to standard tones.

Methods: We acquired data from 14 patients with ALS (13 spinal onset, 1 bulbar), age ranging between 35 to 81 years (mean 63) (10 male, 4 female) and 14 age and sex matched controls. The patients were within first 18 months of diagnosis.

They underwent 128 channel EEG using Biosemi system. MMN was acquired while patients viewed a silent movie to capture their attention. They were presented with a mixture of standard and deviant tones via headphones for 3 blocks each lasting for 7 minutes using presentation software for the oddball experiment.

The results were analyzed using a custom written software in MATLAB and EEGLAB.

Results: MMN in the fronto- central region in scalp was twice in value among patients compared to controls. ($p<0.05$)

Conclusion: MMN is a measure of involuntary attention shift mediated by anterior insular cortex which is part of Salience network. We postulate that increased MMN among ALS patients is secondary to altered network pattern in ALS which can be used as a marker in ALS. Analysis is ongoing among 70 ALS patients to assess whether we could elicit signature changes among ALS subgroups.

Disclosure: Nothing to disclose

P1136

Clinicopathological findings of amyotrophic lateral sclerosis complicated with parkinsonism.

Y. Izumi[1], H. Sumikura[2], K. Fujita[1], H. Nodera[1], T. Kawarai[1], Y. Nishida[3], F. Udaka[4], S. Murayama[2], R. Kaji[1]

[1]Tokushima University Hospital, Neurology, Tokushima, Japan, [2]Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Neuropathology, Tokyo, Japan, [3]Itsuki Hospital, Neurology, Tokushima, Japan, [4]Sumitomo Hospital, Neurology, Osaka, Japan

Background and aims: Amyotrophic lateral sclerosis (ALS) combined with other clinical features (dementia or parkinsonism) is defined as a ALS-Plus syndrome and its rarity has limited detailed neuropathological evaluation.

Methods: We collected 5 cases of ALS who experienced precedent parkinsonism. All the patients underwent a thorough neurological examination as well as brain imaging. Four of the patients died of respiratory failure and underwent autopsy, and one respiratory bounded case underwent skin biopsy.

Results: All patients were without family history of neurodegenerative disorders and resistant to anti-parkinsonism therapies. The average period to death or respiratory support was 12 months after the onset of ALS. Four autopsy cases revealed the following findings consistent with ALS: (1) the corticospinal tracts exhibiting bilateral degeneration; (2) loss of spinal anterior horn cells and gliosis; (3) sparing of posterior columns, Clarke's columns, intermediate lateral columns, and the Onuf's nucleus, and (4) the presence of Bunina bodies in the lower motor neurons and TDP-43-positive neuronal and glial cytoplasmic inclusions throughout the central nervous system. In addition, two cases revealed Lewy bodies and another two revealed tau pathology, which were consistent with Parkinson's disease (PD) and progressive supranuclear palsy (PSP), respectively. The finding of skin biopsy showed Lewy type α-synucleinopathy, suggesting PD.

Conclusion: We describe rare neuropathological combination of ALS and parkinsonism. All patients had rapid progression after onset of ALS. Concurrent presence of TDP43 plus either α-synuclein or tau in an individual might suggest novel pathogenesis of neurodegeneration.

Disclosure: Nothing to disclose

P1137

Biomarker discovery, safety and feasibility of G-CSF compassionate use in ALS patients

S. Johannesen[1], D. Baldaranov[1], A. Khomenko[1], J. Blume[1], J. Kassubek[2], H.-P. Müller[2], I. Kobor[1], T. Bruun[1], J. Grassinger[3], G. Schuierer[4], W. Schulte-Mattler[1], A. Schneider[5], M. Deppe[6], U. Bogdahn[1]

[1]University of Regensburg, Neurology, Regensburg, Germany, [2]University of Ulm, Neurology, Ulm, Germany, [3]University of Regensburg, Hematology and Oncology, Regensburg, Germany, [4]University of Regensburg, Neuroradiology, Regensburg, Germany, [5]Heidelberg, Germany, [6]University of Muenster, Neurology, Muenster, Germany

Background and aims: Granulocyte-colony-stimulating factor (G-CSF) is a long-term established and safe hematopoietic growth factor that may potentially compensate rapid neuronal loss in ALS patients by neuroprotection, increased neurogenesis, neural differentiation. We initiated long-term compassionate use of G-CSF as well as longitudinal follow up of ALS patients and potential biomarkers for patient safety.

Methods: 23 ALS patients (15m, 8f, mean ALS-FRS-r at start 36.75) were treated with G-CSF plus standard therapy. Application modes were individually adapted. Monthly visits with ALSFRS-r, clinical chemistry, and bone marrow mobilization parameters were performed. Pyramidal tract integrity by fractional anisotropy (FA), quantification of motor units by improved Motor Unit Number Index (i-MUNIX), and functional/differentiation markers for stem cells were obtained as biomarkers every 3 months during long-term treatment (> 4 yrs.).

Results: Safety and compliance were excellent, G-CSF was well tolerated. G-CSF resulted in effective hematopoietic stem cell mobilization. Disease progression correlated significantly ($p<0{,}0001$) with i-MUNIX, and as trend with FA. During disease progression patients with lower ALS-FRS-r mobilized less monocytes and CD34+38- stem cells, but more eosinophils. Colony Forming Units for bone marrow stem cell potential were further analyzed. In retrospective analysis a significant decrease in ALS progression rate and clinical relevant prolongation of overall survival of G-CSF patients in comparison to the current Pro-ACT database indicates high safety of prolonged G-CSF treatment.

Conclusion: Long-term administration of G-CSF in ALS patients is safe and feasible. i-MUNIX, FA, and bone marrow differentiation parameters are very promising biomarkers for ALS treatment development. A prospective trial is urgently needed.

Disclosure: Nothing to disclose

P1138

Hirayama disease in Korea

H.E. Lee[1], H.S. Lee[2]

[1]National Health Insurance Service Ilsanhospital, neurology, Seoul, Korea, Republic of, [2]Severance hospital, neurology, Seoul, Korea, Republic of

Background and aims: Hirayama disease (HD), also referred to as juvenile muscular atrophy of distal upper extremity, brachial benign focal amyotrophy, is one of the motor neuron disease but it has benign course. Although HD is frequently reported in Asia, little is known about characteristics of HD in Korea. We analyzed clinical feature, electrophysiological and radiologic findings.

Methods: We retrospectively reviewed the medical records of patients who were diagnosed Hirayama disease accepted according to the proposed criteria (Hirayama et al. 2006).

Results: Total 65 patients were analyzed. The male to female ratio was 31.5. Mean age of symptom onset was 16.97 years. Period of progression was 28.16 months. Unilateral involvement was 55 patients (84.6%) and bilateral involvement was 10 patients (15.4%). Tremor in affective limb was most commonly observed in 30 patients (46.2%), fasciculation was observed in 11 (16.9%) and cold paresis was noted in 7 (10.8%). Muscle atrophy was predominantly hand muscles (96.9%) and forearm muscles (35.4%). The Electrophysiological findings revealed that low compound muscle action potential (CMAP) was found in the median nerve and ulnar nerves in affective limbs. Denervation potentials of electromyography (EMG) were commonly noted in distal muscles. Interestingly, among 55 patients who performed EMG in unaffected arm, 22 patients (40%) had abnormality of EMG. The cervical MRI in neutral position was shown that focal cord atrophy (81.5%), flattening of cervical cord (13.8%) and abnormal curvature (7.7%).

Conclusion: This is the first and the largest study of Hirayama disease in Korea.

Disclosure: Nothing to disclose

P1139

MRI-based cerebellar volume measurements as a biomarker of disease progression of spinocerebellar degeneration

F. Maki, D. Hara, S. Tanaka, R. Sasaki, Y. Hasegawa
St.Marianna University School of Medicine, Department of Internal Medicine Division of Neurology, Kawasaki, Japan

Background and aims: We aimed to explore a suitable method to normalize cerebellar volumes measured by MRI for the evaluation of disease progression of spinocerebellar degeneration (SCD).

Methods: We measured cerebellar volumes using MRI in 12 SCD patients (MSA; 3, CCA; 2, SCA1; 1, SCA3; 3, SCA6; 2, SCA unknown; 1) and 30 controls. All measurements were performed with commercially available software TRI/3D-VOL (RATOC System Engineering, CO.) by means of automatic extraction of cerebellar area with linear interpolation of the slices encompassing the whole cerebellum. Cerebellar volumes were normalized either by anteroposterior diameter of cranium or infratentorial cranial volume. We examined inter-rater variability and test-retest reliability using a dataset obtained from controls and compared correlation coefficients between ICARS and cerebellar volumes normalized by two different methods.

Results: In control subjects, body height, body weight, cranial anteroposterior diameter and infratentorial cranial volume were significantly correlated with cerebellar volumes. Age was not associated with cerebellar volume. Mean cerebellar volumes in male and female were 123.5ml and 108.7ml, respectively (p=0.01). Inter-rater variability was 0.986 and test-retest reliability was 0.988. Effects of volume correction methods using cranial anteroposterior diameter and infratentorial cranial volume were similar. In SCD patients, correlation coefficients between cerebellar volumes corrected by these two methods and total scores of ICARS, were also similar, 0.294 (p=0.000), the other was 0.298 (p=0.000).

Conclusion: MRI-based cerebellar volume corrected by the cranial anteroposterior diameter appeared to be a simple, consistent, reproducible and reliable biomarker of disease progression of SCD.

Disclosure: Nothing to disclose

P1140

Abstract cancelled

Movement disorders 1

P1141

Evaluation of efficacy of opicapone in Parkinson's disease patients with motor fluctuations: phase III, randomized, double-blind, placebo and active-controlled study (BIPARK I)

J. Ferreira[1], A. Lees[2], A. Santos[3], R. Pinto[3], N. Lopes[3], T. Nunes[3], J.F. Rocha[3], P. Soares-da-silva[3]
[1]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [2]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [3]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal

Background and aims: Opicapone (OPC) is a novel once-daily and long-acting peripheral COMT-inhibitor under investigation for Parkinson's disease (PD). The aim of this study was to investigate the efficacy and safety of OPC (5, 25 and 50 mg) compared with entacapone (ENT) and placebo, in levodopa-treated patients with PD and motor fluctuations.

Methods: This was a multinational, 14 to 15-week, double-blind, placebo- and active-controlled study. The primary efficacy variable was the change from baseline in absolute OFF-time based on patient diaries. The key secondary efficacy endpoint was the proportion of OFF- and ON-responders (≥ 1 hour improvement). Safety was assessed by adverse events (AEs), laboratory, vital-signs, ECG, physical and neurological examinations.

Results: 600 patients were randomized to placebo (N=121), 5mg-OPC (N=122), 25mg-OPC (N=119), 50mg-OPC (N=116) or ENT (N=122). Both 50mg-OPC and ENT significantly decreased the OFF-time (1.95 h [p=0.0015] 50mg-OPC and -1.61 h [p=0.0141] ENT vs. -0.93 h placebo) and increased the ON-time without troublesome dyskinesia (1.82 h [p=0.0016] 50mg-OPC and 1.57 h [p=0.0150] ENT vs. 0.78 h placebo). Significantly more patients receiving 25mg- or 50mg-OPC achieved the OFF-time responder endpoint (60.3% [p=0.0464] 25mg-OPC and 69.6% [p=0.0011] 50mg-OPC vs. 47.5% placebo), while 5mg-OPC and ENT missed statistical significance. A significantly higher proportion of ON-responders was also found for the 50mg-OPC group (65.2% [p=0.0028]). OPC and ENT were generally safe and well tolerated.

Conclusion: OPC, particularly 50mg-OPC, was effective in reducing OFF-time in PD patients with a favourable profile compared to ENT.

Disclosure: Nothing to disclose

P1142

Pooled efficacy analysis of opicapone as adjunctive therapy to levodopa in patients with Parkinson's disease and motor fluctuations.

J. Ferreira[1], A. Lees[2], A. Santos[3], N. Lopes[3], R. Costa[3], C. Oliveira[3], R. Pinto[3], T. Nunes[3], J.F. Rocha[3], P. Soares-da-silva[3]
[1]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [2]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [3]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal

Background and aims: The objective of this analysis was to evaluate the efficacy of opicapone (OPC) in patients with Parkinson's disease and motor fluctuations across phase III studies.

Methods: Patient-level data of matching treatment arms of two multicentre, 14 to 15-week, double-blind, randomised, placebo- and active-controlled studies (BIPARK I and II) was integrated (placebo, 25mg-OPC and 50mg-OPC). The studies had similar designs and measurement instruments. The primary efficacy variable was the change from baseline in absolute OFF-time based on patient's diaries. Key secondary measure was the OFF- and ON-time responder rates (≥ 1 hour).

Results: 758 subjects were included in the pooled efficacy set (n=255 placebo, n=241 25mg-OPC, n=262 50mg-OPC). Either 25mg- or 50mg-OPC significantly reduced OFF-time (1.56 h [p=0.0106] 25mg-OPC and -1.94 h [p<0.0001] 50mg-OPC vs. -0.97 h placebo) and increased the ON-time without troublesome dyskinesia (1.43 h [p=0.0083] 25mg-OPC and 1.80 h [p<0.0001] 50mg-OPC vs. 0.72 h placebo). Significantly more patients receiving 25mg- and 50mg-OPC achieved the OFF- and ON-time responders endpoint (60.2% to 64.6% [p<0.005]).

Conclusion: Treatment with OPC is effective in reducing OFF-time and increasing ON-time without troublesome dyskinesia.

Disclosure: Nothing to disclose

P1143

Molecular imaging and psychometric predictors of cognitive outcome in Parkinson's disease: evidences from a 5-year follow-up study

D. Frosini[1], E. Unti[1], C. Pagni[1], M. Giuntini[1], E. Del Prete[1], D. Volterrani[2], U. Bonuccelli[1], R. Ceravolo[1]

[1]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [2]University of Pisa, Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy

Background and aims: Dopamine transporter (DAT) imaging is a diagnostic tool for Parkinson's Disease (PD) but it is also suggested as prognostic marker for motor and non motor outcomes. The ability of coping intersecting pentagons is considered a predictor of cognitive decline. We aimed to evaluate the prognostic role of DAT imaging and pentagon copy for cognitive outcome in a cohort of PD patients with a follow-up of five years.

Methods: 95 de novo PD patients underwent 123I-FP-CIT SPECT at baseline. Striatal indices were calculated with Basal Ganglia Matching Tool. All patients were assessed with UPDRS III for motor impairment and MMSE for cognition at baseline and each year for the five years of follow-up. Occurrence of dementia during the follow-up was recorded.

Results: During the follow-up 18% of patients developed dementia. Patients who developed dementia had lower striatal binding at baseline ($p<0.01$). The frequency of impairment in pentagon copy was significantly higher in PD who developed dementia ($\chi2=9.9, p<0.001$). Binary logistic regression analysis was performed. The model contained two independent variables (striatal uptake and pentagon copy) was statistically significant ($\chi2=20.7, p<0.001$) and as whole it was able to predict the 35% of the variance in cognitive outcome. Both variables independently contributed to the model with an Odd Ratio respectively of 15.9 and 4.9 for low striatal baseline uptake and pentagon copy impairment.

Conclusion: Our findings indicate that DAT imaging performed at baseline and visuospatial and constructional ability as evaluated by pentagon copy intersection test are associated with cognitive outcome in PD patients.

Disclosure: Nothing to disclose

P1144

Advanced neuroimaging techniques to assess brain structural abnormalities in writer's cramp primary dystonia

S. Galantucci[1], F. Agosta[1], L. Sarro[1], A. Tomic[2], P. Valsasina[3], M. Svetel[2], A. Sodero[1], N.D. Kresojevic[2], V.S. Kostic[2], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]University of Belgrade, Clinic of Neurology, Faculty of Medicine, Belgrade, Serbia, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, [1]Neuroimaging Research Unit, Milan, Italy

Background and aims: To investigate cortical and subcortical gray matter (GM) and white matter (WM) patterns of alterations characterizing Writer's Cramp (WC) primary dystonia.

Methods: T1-weighted and diffusion tensor (DT) MRI scans were obtained from 19 WC patients and 30 controls. Surface-based morphometry analysis was used to assess cortical measures. FMRIB-FIRST tool in FSL was used to segment basal ganglia on 3D T1-weighted images; then, volumes and DT MRI metrics were measured for each GM nucleus. TBSS was used to perform a voxel-wise analysis of DT MRI metrics. The effects of disease severity were examined by correlating GM and WM metrics with disease duration and WC severity scales.

Results: Increases in cortical area and volume were found bilaterally in paracentral and postcentral gyri as well as supramarginal and temporo-occipital gyri in WC patients compared with controls. No cortical thickness abnormalities were found. Relative to controls, WC patients did not show significant differences in the basal ganglia volumes, while they showed altered DT MRI metrics of the right caudate, pallidum and putamen. WM microstructural analysis in WC showed increased diffusivities of the corpus callosum and thalamic radiations bilaterally, and right corticospinal tracts and major associative tracts. WCRS score correlated with WM damage of the corpus callosum.

Conclusion: These findings corroborate the hypothesis that WC dystonia is a complex disturbance which results from the involvement of both sensorimotor and associative neural circuits. Advanced MRI techniques may give insight in the pathophysiology of this multifaceted disease.

Disclosure: Nothing to disclose

P1145

Spasmodic dysphonia primary dystonia is associated with cortical and subcortical alterations: a multimodal imaging study

S. Galantucci[1], F. Agosta[1], L. Sarro[1], A. Tomic[2], P. Valsasina[3], M. Svetel[2], A. Sodero[1], N.D. Kresojevic[2], V.S. Kostic[2], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]University of Belgrade, Clinic of Neurology, Faculty of Medicine, Belgrade, Serbia, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, [1]Neuroimaging Research Unit, Milan, Italy

Background and aims: To assess the patterns of cortical and subcortical gray matter (GM) and white matter (WM) damage in patients with Spasmodic Dysphonia (SD) primary focal dystonia.

Methods: T1-weighted and diffusion tensor (DT) MRI scans were obtained from 13 SD patients and 30 controls. TBSS was applied to compare DT MRI indices (i.e., mean [MD], radial [radD] and axial diffusivities, and fractional anisotropy [FA]) between groups on a voxel-by-voxel basis. Cortical measures were analyzed using surface-based morphometry. FMRIB-FIRST tool in FSL was used to segment basal ganglia on T1-weighted images, and volumes and DT MRI metrics of GM nuclei were measured.

Results: Compared with controls, SD patients showed increased MD, radD and decreased FA of the corpus callosum and major WM tracts, mainly in the right hemisphere. Cortical surface analysis showed that SD patients compared to controls had cortical volume increase of the left postcentral, supramarginal and fusiform gyri, while a widespread cortical volume and area decrease was found in the right hemisphere, involving pre- and postcentral gyri and frontal and parietal lobes. SD patients compared to controls did not show significant differences in the basal ganglia volumes, while altered DT MRI metrics were found in right caudate, pallidum and putamen.

Conclusion: Structural alterations in SD patients seem to involve both GM and WM, with different patterns in right and left hemisphere. Such changes may suggest a complex network disorder underlying the pathophysiology of the disease. Advanced neuroimaging studies may give further insight into the understanding of this complex disorder.

Disclosure: Nothing to disclose

P1146

Clinical phenotype and genotype of spinocerebellar ataxia type 3 in a Yemenite Jewish subpopulation

R. Zaltzman[1], R. Sharony[2], C. Klein[1], C. Gordon[1]

[1]Meir Medical Center, Neurology, Kfar Saba, Israel, [2]Meir Medical Center, Genetics, Kfar Saba, Israel

Background and aims: Spinocerebellar ataxia type 3 (SCA-3) has been reported in many ethnic backgrounds with at least four clinical phenotypes. Our objective was to delineate the clinical phenotype and genotype of Yemenite Jewish SCA-3 patients living in Israel.

Methods: Clinical and family pedigrees data of 125 Yemenite Jewish SCA3 patients were collected in our Machado-Joseph Disease Out-patient Clinic. All examined patients underwent a detailed neurological and bedside vestibular examination. For genetic testing, CAG repeats size of the ATXN3 gene was measured, and patients with expanded CAG repeats >44 were diagnosed genetically as having SCA-3.

Results: We were able to associate most of our 125 patients into 17 families. Mean age of disease onset (AO) was 44 years. The most common clinical features were gait, truncal and limb ataxia, dysarthria. Vestibulo-Ocular Reflex (VOR) loss was found in 90% of the patients. The mean number of CAG repeats in the ATXN3 gene of the diseased allele was 67 (range 55 to 76). AO was inversely correlated to the number of CAG repeats (r=-0.7) and was significantly earlier among male patients. Though no genetic anticipation was found, offspring AO was significantly earlier than AO of their parents. In addition, paternal offspring expressed the disease significantly earlier than maternal offspring.

Conclusion: VOR deficit detected on bedside examination should be added as part of the phenotype of Yemenite Jewish SCA-3 patients. Our clinical genetic findings are in partial agreement with other SCA-3 population studies and are relevant in patients‘ management and design of further studies.

Disclosure: Nothing to disclose

P1147

Genetic and phenotypic characteristics of Hungarian patients with Neurodegeneration with Brain Iron Accumulation (NBIA)

Z. Grosz[1], R. Bencsik[2], A. Lengyel[2], A. Gal[2], V. Reményi[3], G. Tamas[1], P. Klivényi[4], M.J. Molnár[2], B. Kalman[5], P. Ács[5]
[1]Budapest, Hungary, [2]Genomic Medicine and Rare Disorders, Budapest, Hungary, [3]Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary, [4]University of Szeged, Department of Neurology, Szeged, Hungary, [5]University of Pécs, Pécs, Hungary

Background and aims: NBIA is a neurodegenerative disease causing progressive movement disorder. In the past decade it underwent a great deal of change and became a dynamically developing field of the neurodegenerative disorders. Due to several genetic alteration have been found classification had to be laid on new bases, and still many expected to be on the way. Symptoms may vary on a wild spectra even in the same subgroup of NBIA. The factors that influence disease severity and rate of progression are unknown.

Methods: Patients with movement disorders and MR signs of distinct iron deposition were tested to the whole coding regions of PANK2, PLA2G6, MPAN and CP genes by direct Sanger sequencing. Copy number variations were tested by MLPA. Detected mutations were analyzed by Polyphen2, SIFT, Mutation Assessor, LRT softwares.

Results: Pathogenic mutations were detected 17 out of 36 NBIA patients. 37.5% of them were MPAN mutations, which is higher proportion than reported in the literature. Others were PANK2 (5 patients), ceruloplazmin (3 patients) and PLA2G6 (3 patients) gene mutations. Some subgroups have hallmark features but clinical spectra varies on a broad spectrum between patients even in the same subgroup.

Conclusion: In Hungary MPAN mutations are the most common. Even in mild cases with extrapyramidal symptoms suspicious to NBIA genetic testing should be considered.

Disclosure: The study was supported by the National Brain Research Program.

Movement disorders 2

P1148

Peripheral neuropathy in Parkinson's disease: an in vivo confocal microscopy study

L. Vieira[1], R. Anjos[1], A. De Sousa[2], N. Silva[1], A.L. Basílio[1], V. Santos Maduro[1], N. Alves[1], P. Candelária[1]
[1]Centro Hospitalar de Lisboa Central, Ophthalmology, Lisbon, Portugal, [2]Centro Hospitalar de Lisboa Central, Neurology, Lisbon, Portugal

Background and aims: Peripheral neuropathy (PN) has been described in patients with Parkinson's disease (PD) treated with dopaminergic therapy. Corneal confocal microscopy (CCM) provides in-vivo imaging of corneal nerve fibers and has been used to analyze nerves alterations in a variety of ocular diseases, after corneal surgery and in systemic diseases, like diabetes. The purpose of our study is to analyze corneal sensation and whether CCM can detect alterations in corneal nerve morphology in patients with PD.

Methods: A prospective case-control study was conducted in ten patients with PD (under long-term dopaminergic medication) and ten age and sex-matched healthy subjects. Patients underwent neurological and complete ophthalmological evaluation. Corneal sensitivity testing was performed with a Cochet-Bonnet esthesiometer and corneal sub-basal nerve morphology assessment with CCM (Heidelberg Retina Tomograph II/Rostock Cornea Module).

Results: Patients with PD had decreased corneal sensation in comparison with control group. Corneal nerve fiber morphology differed between the groups: PD patients had lower nerve fiber density, nerve fiber length and nerve branch density and higher nerve tortuosity comparatively to healthy subjects ($p<0.05$).

Conclusion: As far as we know, this is the first study to detect corneal sub-basal nerve changes in patients with PD. CCM may be used to detect signs of PN and follow patients doing dopaminergic therapy.

Disclosure: Nothing to disclose

P1149

Are magnetic resonance imaging features of the nigrostriatal system biomarkers for Parkinson's disease?

L. Hopes[1], G. Grolez[1], C. Moreau[1], R. Lopes[2], G. Rychewaert[1], N. Carriere[1], F. Auger[3], C. Laloux[4], M. Petrault[4], J.-C. Devedjian[4], M.M.P.R. Bordet[5], L. Defebvre[6], P. Jissendi[2], C. Delmaire[2], D. Devos[6]
[1]Department of Movement Disorders and Neurology, Lille University Hospital, Lille University, Lille, France, Lille, France, [2]Department of Neuroradiology, Lille Nord de France University, CHU Lille, Lille, France, Lille, France, [3]IMPRT, Plateforme d'imagerie du vivant, Université de Lille [2], Lille, France, [4]Lille University, Lille, France, [5]INSERM U[1171], Faculty of Medicine, Lille University, Lille, France, Lille, France, [6]Lille, France

Background and aims: Magnetic resonance imaging (MRI) can be used to identify biomarkers in Parkinson's disease (PD); higher R2* values reflect iron overload and thus high levels of oxidative stress, whereas volume and/or shape changes reflect neuronal death. We sought to assess iron overload in the nigrostriatal system and characterize its relationship with focal and overall atrophy of the striatum in the pivotal stages of PD.

Methods: 20 control participants and 70 PD patients at different disease stages (untreated de novo patients, treated early-stage patients and advanced-stage patients with L-dopa-related motor complications) were included in the study. We determined the R2* values in the substantia nigra (SN), putamen and caudate nucleus, together with striatal volume and shape analysis. We also measured R2* in a MPTP mouse model and two years later in the early-stage PD patients.

Results: The R2* values in the SN, putamen and caudate nucleus were significantly higher in de novo PD patients than in controls. Early-stage patients displayed significantly higher R2* values in the SN (with changes in striatal shape), relative to de novo patients. Measurements after a two-year follow-up in patients and characterization of the acute MPTP mouse model confirmed that R2* changed rapidly with disease progression. Advanced-stage patients displayed significant atrophy of the putamen and caudate nucleus, relative to earlier disease stages.

Conclusion: Each pivotal stage in PD appears to be characterized by putative MRI biomarkers in the nigrostriatal region: iron overload at the de novo stage, striatal shape changes at early-stage disease and generalized striatal atrophy at advanced disease.

Disclosure: Nothing to disclose

P1150

Correlation between MRI-based cerebellar volume and severity of ataxia as evaluated by ICARS in subtypes of spinocerebellar degeneration.

D. Hara, S. Tanaka, F. Maki, R. Sasaki, Y. Hasegawa
St.Marianna University School of Medicine, Department of Internal Medicine Division of Neurology, Kawasaki, Japan

Background and aims: Progression of clinical symptoms and cerebellar atrophy may vary among subtypes of spinocerebellar degeneration (SCD) and multiple system atrophy (MSA).To explore a sensitive biomarker for predicting disease progression in individual patients with SCD and MSA, we investigated correlations between MRI-based cerebellar volume and the International Cooperative Ataxia Rating Scale (ICARS) among different clinical subtypes on a cross-sectional basis.

Methods: MRI-based cerebellar volume and ICARS score were evaluated in 52 SCD patients (CCA:18, SCA1 :3, SCA2 :3, SCA3: 7, SCA6 :13, SCA31:2 unknown type: 6) and 34 MSA patients. Cerebellar volumes were measured by TRI/3D-VOL (RATOC System Engineering Co) software using DICOM data. For the statistical analysis, volume index (Vdx) was used, which was a cerebellar volume normalized by anteroposterior diameter of cranium.

Results: Significant correlation between ICRAS total score and Vdx was observed in all disease subtypes (Y=-0.002X + 0.016, Spearman's Ro=-0.322, p=0.000). ICARS domain I and II were also significantly correlated with Vdx (Ro=-0.36 [p=0.000] and Ro=-0.214 [p=0.003]), but domain III and IV were not. Correlation coefficient varied among patients with different subtype, Ro=0.632 (p=0.000) in MSA, Ro=0.545 (p=0.005) in SCA6. Significantly correlation was not observed in SCA (1,2,3,31, other) and CCA.

Conclusion: In SCD patients ICARS total score, ICARS domain I and II were significantly correlated with cerebellar volume normalized by anteroposterior diameter of cranium, especially in patients with MSA and SCA6.

Disclosure: Nothing to disclose

P1151

The state of the sensory afferentation in patients with writer's cramp

V. Hleb, S. A. Likhachev, G. Zabrodzets, T. Charnukha
Minsk, Belarus

Background and aims: To evaluate the state of the sensory afferentation in patients with writer's cramp (WC).

Methods or Materials or Case Report: Somatosensory evoked potentials were recorded using the diagnostic complex VikingSelect, Nicolet (USA). We studied 42 patients with WC (age 38.5±4.6 years, duration of disease - 5.3±0.64 years, the ratio of men and women – 1.36:1, the dominant hand was the right hand) and control group of 30 healthy volunteers (age 38.5±4.6 years, the ratio of men and women – 1,36:1, the dominant hand was the right hand) (p>0.05). We investigated the variation of the peak-to-peak amplitude N20/P24, peak-to-peak latency N13/P20 and differences of these parameters between the right and left hands in patients with WC.

Results: The value of the peak-to-peak amplitude N20/P24 at C3'/C4' was 1,73 [0.20; 2.29] (median [25%; 75%]) in the study group and 2.12 [1.19; 3.94] in the control group, decrease in the peak-to-peak amplitude was statistically significant (p=0.035). There was no significant difference in peak-to-peak latency N13/P20 in patients with WC compared with the control group (P>0.05) and in the amplitude N20/P24, latency N13/P20 in the right and left hands in patients with WC and control (P>0.05).

Conclusion: These results support the view that somatosensory evoked potentials can be used to investigate the dysfunction of the sensory afferentation in patients with WC. The present study shows that the WC is accompanied not only by the motor dysfunction, but also by the dysfunction of the sensory afferentation according to somatosensory evoked potentials.

Disclosure: Nothing to disclose

P1152

Abstract cancelled

P1153

Neurodegeneration with Brain Iron Accumulation type I: clinical, genetic, radiographic delineation and impact on quality of life

J. Jesus Ribeiro, M. Sousa, M. Tábuas-Pereira, M. Baptista, F.V. Moreira, C. Januário

Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Background and aims: Neurodegeneration with brain iron accumulation (NBIA) type I is one of the major subtypes of a group of disorders characterized by basal ganglia iron deposition.The development of new techniques of genetic sequencing and neuroimaging allows to delineate the different phenotypes of NBIA type I and it is essential to establish the impact on the quality of life in such patients.

Methods: 9 patients with clinical features consistent with NBIA type I, evaluated with Fahn-Marsden Dystonia Rating scale (FMDRS), underwent genetic testing and performed magnetic resonance imaging (MRI). Quality of life was assessed with Parkinson's Disease Questionnaire (PDQ-39).

Results: 80% of our patients had late-onset disease (mean age 20 years ± 2.4). The most common presenting sign was dystonia, mainly blepharospasm. We obtained a Pearson correlation of 0.893 ($p = 0.003$) between total scores of FMDRS and PDQ-39. All patients had mutations in the gene encoding pantothenate kinase 2 (PANK2), 63% in homozygosity. 8 patients showed the sign „eye of the tiger" on MRI but one of them, homozygous for a PANK2 gene mutation, did not present this typical sign even later during the course of the disease.

Conclusion: Dystonia was the most common extrapyramidal feature. There was a strong correlation between the degree of dystonia and impact on quality of life. The missense mutation more frequently detected was c.1070G>C (p.Arg357Pro), common in the Portuguese population. Unlike several published reports, the "eye of the tiger" sign did not present an absolute correlation with PANK2 mutations.

Disclosure: Nothing to disclose

P1154

Decreased cerebrospinal fluid levels of chromogranin A in early stages of Parkinson's disease may predict earlier development of orthostatic hypotension

M. Kaiserova[1], H. Prikrylova Vranova[1], J. Galuszka[2], D. Stejskal[3], K. Mensikova[1], J. Zapletalova[4], J. Mares[1], P. Kanovsky[1]

[1]Faculty of Medicine and Dentistry, Palacky University and University Hospital, Department of Neurology, Olomouc, Czech Republic, [2]Faculty of Medicine and Dentistry, Palacky University and University Hospital, Department of Internal Medicine I - Cardiology, Olomouc, Czech Republic, [3]Central Moravian Hospital County Inc., Department of Laboratory Medicine and Department of Medicine, Prostejov, Czech Republic, [4]Faculty of Medicine and Dentistry, Palacky University and University Hospital, Department of Medical Biophysics, Olomouc, Czech Republic

Background and aims: Orthostatic hypotension (OH) in Parkinson's disease (PD) is probably caused by pronounced vasomotor and cardiac sympathetic dysfunction. CgA is co-released from vesicles together with catecholamine hormones and is frequently localized within neurons of the rostral ventrolateral medulla oblongata (RVLM). About two-thirds of RVLM neurons express a catecholaminergic phenotype (C1 cells). These cells are critical for the full expression of sympathoexcitatory responses generated by the RVLM. There is a selective loss of C1 adrenergic neurons in PD patients. The aim of the study was to test the hypothesis of an association between the CSF chromogranin A (CgA) level and blood pressure changes during the upright position on a tilt table.

Methods: 20 L-DOPA-naïve patients in the early stage of PD and twenty controls were involved. All patients underwent CSF examination, head-up tilt table test and electromyography of the lower limbs.

Results: CSF CgA levels were significantly lower in the patients with PD than in the controls (median 86.0 vs. 141.0, $P = 0.001$). There was a significantly positive correlation between the CSF CgA level and diastolic blood pressure change (Pearson correlation 0.717; Sig (2-tailed) 0.0004). The CSF CgA levels were lower in patients with OH compared to patients without OH (median 52 vs. 121.6; $P = 0.002$).

Conclusion: This study may help to clarify the mechanism of orthostatic dysregulation in PD patients. Decreased CSF CgA level may indicate an increased risk for the development of orthostatic hypotension in the earlier stages of PD.

Disclosure: This study was supported by the grant projects IGA MZ CR NT-12221, IGA_LF_2014_018

P1155

Functional (psychogenic) movement disorders of the eyes, face, and tongue.

D. Kaski[1], A. Bronstein[1], M. Edwards[2], J. Stone[3]
[1]Imperial College London, London, United Kingdom, [2]Institute of Neurology, London, United Kingdom, [3]University of Edinburgh, Edinburgh, United Kingdom

Background and aims: Functional (psychogenic) neurological symptoms are commonly encountered in neurological practice. Eye, face and tongue movement disorders are a frequent but perhaps under-recognized feature of patients with functional symptoms.

Methods: A literature and personal database review of the common symptoms and signs of cranial functional movements with a focus on the eyes (convergence spasm, voluntary nystagmus, convergence paralysis, and functional limitation of gaze), face and tongue (eyelid closure, mouth deviation, platysma contraction, and tongue deviation).

Results: We describe the common symptoms and signs of functional movement disorders affecting the eyes, face, and tongue. In functional eye movement disorders ocular movements may be normal during the casual examination, becoming abnormal when the eyes are formally assessed. Several distinctive features point towards a functional facial movement disorder; for example, platysma is commonly contracted which leads to the corner of the mouth being pulled down on one side. This is why this particular symptom is commonly misattributed to stroke.

Conclusion: Identification of a functional eye and facial movement disorder is aided by looking for positive features in the examination, and in particular the casual examination. Failure to correctly classify and diagnose functional disorders may lead to significant iatrogenic damage, perpetuate illness beliefs and deny the patient the appropriate treatment.

Disclosure: Nothing to disclose

P1156

Assessment of the quality of life of caretakers who looked after patients with Parkinson's disease

M. Khanova
Tashkent, Uzbekistan

Background and aims: Objective: to assess the quality of life of caretakers who looked after patients with PD and to identify factors influencing negatively on their lives.

Methods: We consecutively examined 50 pairs of PD patients and their caretakers. Caregiver Burden Inventory (CBI) was used to assess the burden of PD on the caretakers. To assess the influence of PD on the caretakers we used: the United Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr Scale (H-Y Scale), the Activity of Daily Living Scale (ADL), the Parkinson's Disease Questionnaire (PDQ-39), the Wakefield Depression Rating Scale (WDRS), the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE).

Results: According to the data of investigations, ADL and PDQ-39 (P=0.001), as well as the age of the caretakers (40.5±4.2 years, P=0.002) were the main predictors of CBI. According to WDRS, 54% of caretakers has depression. 33% and 26% of patients had cognitive dysfunctions in MMSE and MoCA, respectively.

Conclusion: Many factors might comprehensively affect the burden of PD on caretakers of the patients. Attention needs to be given to the early identification of factors that generating stress on caretakers in order to improve their quality of life.

Disclosure: Nothing to disclose

MS and related disorders 1

P1157
Abstract cancelled

P1158
The efficacy and safety of daclizumab high-yield process (DAC HYP) in patients previously treated with disease-modifying therapies: subgroup analyses from the DECIDE study

E. Havrdova[1], L. Kappos[2], K. Selmaj[3], D.L. Arnold[4], A. Boyko[5], M. Kaufman[6], H. Wiendl[7], J. Rose[8], S. Greenberg[9], M. Sweetser[10], P. Wang[10], L. Barbato[10]
[1]First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]University Hospital Basel, Basel, Switzerland, [3]Medical University of Lodz, Lodz, Poland, [4]NeuroRx Research and Montreal Neurological Institute , Montreal, Canada, [5]Russian Research and Science Medical University named by Pirogov, MMSC, Moscow, Russian Federation, [6]Cole Neurological Institute, University of Tennessee - Knoxville, Knoxville, TN, USA, [7]University of Münster, Münster, Germany, [8]University of Utah Department of Neurology and the Neurovirology Research Laboratory, VASLCHCS, Salt Lake City, UT, USA, [9]AbbVie Biotherapeutics Inc., Redwood City, CA, USA, [10]Biogen Idec, Cambridge, MA, USA

Background and aims: The DECIDE study demonstrated the efficacy and safety of DAC HYP compared with intramuscular interferon beta-1a (IFN beta-1a) in patients with relapsing-remitting multiple sclerosis (RRMS). The objective of these analyses was to evaluate the efficacy and safety of DAC HYP versus IFN beta-1a in patients participating in DECIDE who had previously been treated with disease-modifying therapies (DMT) for MS.

Methods: Patients (age 18–55 years; Expanded Disability Status Scale 0–5) were randomised to subcutaneous DAC HYP 150mg every 4 weeks or intramuscular IFN beta-1a 30mcg once weekly for 96–144 weeks. Primary and secondary efficacy endpoints and safety were analysed in patients who had received treatment with interferon beta, glatiramer acetate or other DMT for MS, excluding steroids, before enrollment in DECIDE.

Results: 380/919 (41%) patients in the DAC HYP group and 376/922 (41%) patients in the IFN beta-1a group had previously been treated with DMT for MS. The point estimates for each of the primary and secondary study endpoints favoured DAC HYP compared with IFN beta-1a (Table). Among patients previously treated with DMT for MS, infections were observed in 73% and 62%, skin and subcutaneous tissue disorders in 43% and 22%, and elevations of alanine/aspartate aminotransaminases in 8%/6% and 7%/5% of patients in the DAC HYP group and IFN beta-1a group, respectively.

Efficacy end point	DAC HYP (95% CI)	IFN beta-1a (95% CI)	Difference (95% CI)
Adjusted ARR (primary endpoint)	0.258 (0.214, 0.312)	0.401 (0.336, 0.479)	RR: 0.644 (0.518, 0.801)
Adjusted mean number new/newly enlarging T2 hyperintense lesions	4.32 (3.56, 5.25)	9.00 (7.36, 11.00)	% reduction: 52.0% (38.4, 62.6)
Patients with 3-month confirmed disability progression at 144 weeks, %	21.3	28.7	HR: 0.79 (0.57, 1.10)
Patients relapse free at 144 weeks, %	56.7	44.1	HR: 0.72 (0.58, 0.90)
Patients with worsening (≥7.5 points) in MSIS-29 physical scale at 96 weeks, %	22.5	25.8	OR: 0.83 (0.59, 1.16)

ARR, annualised relapse rate; CI, confidence interval; HR, hazard ratio; MSIS-29, Multiple Sclerosis Impact Scale; OR, odds ratio; RR, rate ratio.

Conclusion: The results of these subgroup analyses reflect the overall findings from DECIDE and demonstrate the efficacy and safety profile of DAC HYP compared with IFN beta-1a in patients previously treated with DMT for MS.

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P1159

Teriflunomide (Aubagio[R]) pregnancy registry: design and enrolment procedures for pregnant women with multiple sclerosis exposed to teriflunomide

K. Hellwig[1], C. Lebrun-Frenay[2], D. Rog[3], M. Benamor[4], S. Tcherny-Lessenot[4], P. Truffinet[4], A. Ghezzi[5]

[1]St. Josef Hospital at Ruhr University Bochum, Bochum, Germany, [2]Hôpital Pasteur, Nice, France, [3]Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [4]Genzyme, a Sanofi company, Chilly-Mazarin, France, [5]Ospedale di Gallarate, Gallarte, Italy

Background and aims: Teriflunomide, approved for treatment of relapsing-remitting multiple sclerosis (MS), is contraindicated for use in pregnancy, based on signs of developmental toxicity in rats and rabbits. During teriflunomide clinical trials, pregnancies occurred without signs of structural or functional deficits in newborns, but were too few to exclude reproductive toxicity. Therefore, it is important to continue to collect data regarding teriflunomide exposure in pregnancy. The International Teriflunomide Pregnancy Exposure Registry will compare birth defects (congenital malformations, foetal deaths, termination due to foetal anomaly) in teriflunomide-exposed pregnant women with those reported by the European Surveillance of Congenital Anomalies (EUROCAT).

Methods: The registry is a voluntary, multinational, prospective, observational, exposure-registration study. Pregnant women with MS with teriflunomide exposure (any dose any time after day 1 of last menstrual period until pregnancy end) can enrol. National Coordinators will liaise with healthcare professionals to collect information on teriflunomide-exposed pregnancies and coordinate patient enrolment in the registry. The registry will recruit 196 women to achieve 104 live births, providing 80% power to detect a 3.95-fold increase in risk ratio of birth defects associated with teriflunomide exposure vs EUROCAT. Pregnancy outcome data including birth defects and infant characteristics during the first year of life will be collected.

Results: Enrolment commenced early 2015 and will continue until December 2019. Interim results will be reported when available.

Conclusion: This registry aims to provide data on pregnancy outcomes and infant development during the first year of life from teriflunomide-exposed pregnancies, and will help physicians provide better counselling for women exposed to teriflunomide during pregnancy.

Disclosure: Study supported by Genzyme, a Sanofi company.

P1160

Five-year follow-up of delayed-release dimethyl fumarate in RRMS: integrated clinical efficacy data from the DEFINE, CONFIRM, and ENDORSE Studies

M. Hutchinson[1], R. Gold[2], R.J. Fox[3], J.T. Phillips[4], A. Bar-Or[5], L. Kappos[6], S. Sheikh[7], R. Zhang[7], M. Yang[7], N.C. Kurukulasuriya[7]

[1]St. Vincent's University Hospital, Dublin, Ireland, [2]St. Josef Hospital, Ruhr University, Bochum, Germany, [3]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, USA, [4]Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, USA, [5]Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada, [6]University Hospital, Basel Neurology, Basel, Switzerland, [7]Biogen Idec, Inc., Cambridge, USA

Background and aims: Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated efficacy and acceptable safety in patients with relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies; ENDORSE is an 8-year extension of DEFINE/CONFIRM. We report long-term (5-year minimum follow-up) clinical efficacy outcomes with DMF.

Methods: Patients randomised to DMF 240 mg twice (BID) or three times daily (TID) in DEFINE/CONFIRM continued the same dosage in ENDORSE. Patients randomised to placebo (PBO; DEFINE/CONFIRM) or glatiramer acetate (GA; CONFIRM) were re-randomised 1:1 to DMF 240 mg BID or TID. Data were analysed (14 May 2014 cutoff) by treatment arm in parent/extension study. Results for the approved dosage of DMF (240 mg BID) are reported.

Results: Of 2,079 patients completing DEFINE/CONFIRM, 1,736 were dosed in ENDORSE, including 501 BID/BID, 249 PBO/BID, and 118 GA/BID patients. With continuous DMF (BID/BID), adjusted annualised relapse rates (ARRs) remained low over five years (two years parent study; three years ENDORSE). Low ARRs were also observed in ENDORSE among patients switched from PBO or GA (Table). Low proportions of patients were estimated to have disability progression (24-week confirmed Expanded Disability Status Scale progression) at 5 years in the BID/BID, PBO/BID, and GA/BID groups (0.186 [95% confidence interval, CI, 0.153–0.224], 0.211 [95% CI, 0.162–0.271], and 0.257 [95% CI, 0.184–0.352], respectively).

Table. Adjusted ARR by year

Adjusted ARR (95% CI)	DEFINE/CONFIRM		ENDORSE		
	Year 1	Year 2	Year 3	Year 4	Year 5
BID/BID (n=501)	0.202 (0.162–0.252)	0.163 (0.128–0.208)	0.139 (0.105–0.184)	0.143 (0.109–0.188)	0.138 (0.104–0.183)
PBO/BID (n=249)	0.345 (0.269–0.444)	0.280 (0.213–0.368)	0.176 (0.121–0.255)	0.131 (0.086–0.198)	0.107 (0.068–0.171)
GA/BID (n=118)	0.295 (0.203–0.430)	0.182 (0.114–0.291)	0.182 (0.109–0.302)	0.137 (0.077–0.245)	0.118 (0.062–0.225)

Conclusion: Treatment with DMF was associated with low relapse rates and low disability progression over 5 years. Results support the use of DMF as a long-term treatment for patients with RRMS.

Disclosure: Study supported by: Biogen Idec

P1161

Natalizumab discontinuation is associated to a rebound of cognitive impairment in multiple sclerosis patients

P. Iaffaldano, R.G. Viterbo, D. Paolicelli, V. Direnzo, M. D'Onghia, M. Trojano

University of Bari, Department of Basic Medical Sciences, Neurosciences and Sense Organs, Bari, Italy

Background and aims: Clinical and radiological disease reactivation has been described after Natalizumab(NTZ) discontinuation. Whether this disease reactivation involves also cognitive functions is not known to date. The aim of this work was to evaluate the effect of NTZ suspension on cognitive functions.

Methods: Patients underwent a neuropsychological evaluation using the Brief Repeatable Battery (BRB), and the Stroop Test (ST) at baseline, during NTZ treatment and after 1 year of NTZ discontinuation. The Cognitive Impairment Index (CII) as a measure of global cognitive function was calculated for each patient. The annualized-relapse-rate (ARR) and the number of gadolinium enhancing lesions (GD) were recorded for each patient, before, during and after the NTZ treatment.

Results: In 82 RRMS patients , baseline ARR(1.90±0.85 vs 0.30±0.56), number of GD lesions (1.3±1.72 vs 0.17±0.49), and CII (14.11±6.79 vs 10.61±7.06) significantly ($p<0.0001$) decreased during NTZ treatment. Twenty-eight of these patients interrupted NTZ treatment and were evaluated for a 1-year period (12.87±7.62 months) after treatment suspension. At the end of this period the ARR (0.50±0.64 vs 0.93±0.86, $p=0.042$), the number of GD lesions (0.18±0.48 vs 0.54±0.51, $p=0.004$) and the CII (9.79±8.16 vs 12.86±7.72, $p<0.0001$) showed a significant increase.

Conclusion: The beneficial effect of NTZ on cognitive functions is lost after the discontinuation of the drug. The rebound of the cognitive impairment after NTZ discontinuation goes in parallel with the clinical and radiological disease reactivation. Our data reinforce the hypothesis that, in the short-term, NTZ exerts its positive impact on cognitive functions by means of its anti-inflammatory properties.

Disclosure: Nothing to disclose

P1162

Teriflunomide hair photography project: analysis by a dermatologist

a. Jackson[1], L. Hendin Travis[2], A. Okai[3], L. Farnett[4], S. Cavalier[4], D. Stam[4], K. Liu[4], K.R. Edwards[5]

[1]Baton Rouge Clinic, Baton Rouge, USA, [2]Phoenix Neurological Associates Ltd, Phoenix, USA, [3]Multiple Sclerosis Treatment Center of Dallas, Dallas, USA, [4]Genzyme, a Sanofi company, Cambridge, USA, [5]Multiple Sclerosis Center of Northeastern New York, Latham, USA

Background and aims: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS. In phase 3 trials, 13% of patients receiving teriflunomide 14 mg experienced hair thinning compared with 4% receiving placebo. Teriflunomide-associated hair thinning is likely due to telogen effluvium, a type of hair loss caused by premature transition of follicles to the resting phase. Here, photographs of self-reported hair thinning are analysed from a dermatological perspective.

Methods: Patients who reported hair thinning to health care professionals (HCPs) during teriflunomide treatment were eligible for inclusion. At onset and resolution, HCPs completed hair thinning questionnaires, ranking patient-perceived severity from 0 to 10. With a standardized protocol and camera, patients were photographed from 5 standard views (anterior, posterior, left lateral, right lateral, anterior superior) and an optional manipulated view with hair pulled back. The severity of hair loss will be classified from a dermatological perspective.

Results: At presentation, all of the 31 cases were classified by HCPs as mild or moderate. Follow-up visits took place on average 268 days (9 months) after onset of hair thinning. Complete/near-complete resolution or marked improvement was reported in 26/31 patients at follow up. Results from the dermatological analysis will be presented.

Conclusion: Hair thinning in these patients was consistent with observations from the clinical trial programme: cases were usually mild and most patients recovered fully. Dermatological classification of teriflunomide-associated hair thinning will help HCPs to inform patients' expectations in advance of treatment.

Disclosure: Study supported by Genzyme, a Sanofi company.

P1163

Periventricular lesion burden in multiple sclerosis correlates with cortical thinning

M. Jehna[1], L. Pirpamer[2], M. Khalil[2], F. Stulnig[2], S. Fuchs[2], S. Ropele[2], C. Langkammer[2], A. Pichler[2], H. Deutschmann[1], F. Fazekas[2], C. Enzinger[2]

[1]Medical University of Graz, Department of Radiology, Graz, Austria, [2]Medical University of Graz, Department of Neurology, Graz, Austria

Background and aims: It has been suggested recently that cortical pathology in multiple sclerosis (MS) may at least partly be caused by factors in the cerebrospinal fluid (CSF). We thus hypothesised that MS related tissue changes in compartments close to the CSF such as periventricular lesions might correlate with cortical pathology.

Methods: We investigated 91 patients with a clinically isolated syndrome (CIS) and 69 patients with relapsing-remitting MS (RRMS) (mean age: CIS: 31.4±9.0; RRMS: 33.0±8.7 years, mean disease duration: CIS: 7.2±15 months; RRMS: 8.0±6.5 years, median EDSS: CIS: 1, 0-3.5; RRMS: 1.25, 0-4) with 3.0T MRI. MS lesions were semi-automated segmented on the FLAIR images. To quantify periventricular lesion load (PV-LL), we generated ventricle masks and dilated them by a voxel factor of 3. Lesions within the dilated ventricle margin were classified as periventricular. Cortical pathology was assessed via cortical mean thickness (CMT) and compared to data from 59 healthy controls (HC) (mean age: 29.1±7.4 years).

Results: Compared to HC, CIS and RRMS patients demonstrated significantly reduced CMT (Figure 1). Even after controlling for ventricular atrophy, increased periventricular lesion occupancy (percentage of PV-LL) significantly correlated with decreased CMT in RRMS (r: -0.314, p=0.009) but not in CIS (r: 0.016, p=0.882) patients (Figure 2).

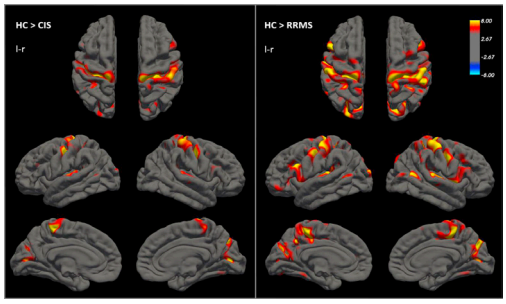


Figure 1: Differences in cortical thinning between HC and CIS (on the left) and HC and RRMS (on the right).

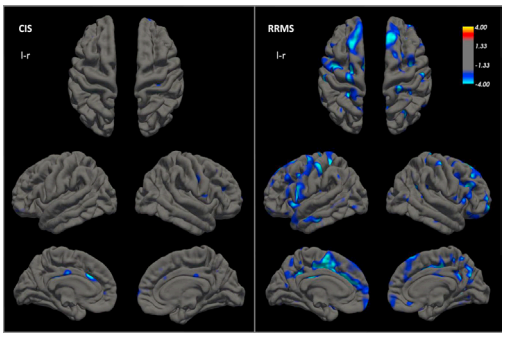


Figure 2: Correlation between increased PV-LL and reduced CMT in CIS (on the left) and RRMS (on the right).

Conclusion: The correlation between increased periventricular lesion burden and decreased CMT suggestive of subpial cortical pathology supports the concept that common CSF-mediated factors might play a role in the accumulation of brain damage in MS, particularly in patients with relapsing-remitting inflammation.

Disclosure: This study was funded by the Austrian MS-research society (Vienna, Austria).

P1164

Autoantibodies of MS patients recognizing brain lipids react mainly with cholesterol

A. Jurewicz[1], M. Domowicz[1], G. Galazka[1], A. Ewiak-Paszynska[1], C. Raine[2], K. Selmaj[1]

[1]Medical University of Lodz, Department of Neurology, Lodz, Poland, [2]Albert Einstein College of Medicine, Department of Pathology, New York, USA

Background and aims: Increasing data indicate that lipids might induce autoimmune responses and determine the course of multiple sclerosis (MS).

Methods: Lipid fractions isolated by Folch procedure from MS and control brains, characterized by thin layer chromatography (TLC) were used as antigens in ELISA assays with serum of RR-MS patients (n=10) and control patients (n=10). In control set of experiments serum immunoreactivity with synthetic lipids: L-α-lysophophatidylocholiline, cholesterol, galactocerebrosides, β2-glycoprotein 1 (β2-GP1) and cardiolipin was assessed. To confirm antibody binding specificity, IgG and IgM were purified by affinity (IgG) or exclusion chromatography (IgM), digested with pepsin and papain and used for ELISA.

Results: As assessed by TLC, in MS brains dominated neutral lipids and all lipid fractions contained cholesterol esters. In control brains dominated phospholipids and cholesterol esters were scarcely present. IgG and IgM of MS serum bound to almost all lipid fractions with higher efficacy than IgG and IgM of control serum. To assess the specificity of lipid binding by MS serum, purified IgG and IgM, were digested and generated F(ab)2 fragments showed high binding to lipid fractions in contrary to Fc fragments. To further characterize lipids recognized by MS serum synthetic lipids were used as antigen in ELISA assays. Only cholesterol was found to bind IgG and IgM with high efficacy. Preabsorbtion of MS serum with cholesterol significantly decreased subsequent IgG and IgM recognition of lipid fractions by up 70% confirming specific cholesterol recognition by serum of MS patients.

Conclusion: These results indicate that IgG and IgM of MS serum specifically recognize cholesterol.

Disclosure: Nothing to disclose

P1165

Five-year follow-up of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: MRI outcomes from DEFINE, CONFIRM, and ENDORSE

T. Yousry[1], D.L. Arnold[2], R.J. Fox[3], R. Gold[4], E. Havrdova[5], L. Kappos[6], D. MacManus[1], S. Sheikh[7], R. Zhang[7], M. Yang[7], N.C. Kurukulasuriya[7]

[1]University College London Institute of Neurology, Queen Square Multiple Sclerosis Centre, NMR Research Unit, London, United Kingdom, [2]NeuroRx Research, Montreal Neurological Institute, McGill University, Montreal, Canada, [3]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, USA, [4]St. Josef Hospital, Ruhr University, Bochum, Germany, [5]Department of Neurology, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [6]University Hospital, Basel Neurology, Basel, Switzerland, [7]Biogen Idec, Inc., Cambridge, USA

Background and aims: ENDORSE is an 8-year extension of the 2-year DEFINE/CONFIRM studies that demonstrated efficacy and safety of delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) in patients with relapsing-remitting multiple sclerosis. We report long-term (5-year minimum follow-up) integrated magnetic resonance imaging (MRI) outcomes with DMF.

Methods: Patients initially randomised in DEFINE/CONFIRM to DMF 240 mg twice (BID) or three times daily (TID) continued the same dosage in ENDORSE; patients randomised to placebo (PBO) or glatiramer acetate (GA) were re-randomised 1:1 to DMF BID or TID. Brain MRI scans were obtained yearly in ENDORSE from an MRI cohort. Data for DMF BID (as of 14 May 2014) are reported.

Results: Of 982 MRI cohort patients completing DEFINE/CONFIRM, 746 received treatment in ENDORSE; 363 received DMF BID (211 BID/BID, 104 PBO/BID, 48 GA/BID). Among the 152 BID/BID patients remaining after 5 years' follow-up, 63% were free of new/enlarging T2 lesions and 73% were free of new T1 hypointense lesions during Year 3 of ENDORSE; 88% were free of gadolinium-enhancing lesions at ENDORSE Year 3 scan. MRI outcomes (T2 lesions) by yearly interval are reported for BID/BID patients and patients who switched to DMF (Table).

Table. Proportion of patients with no new/enlarging T2 lesions by yearly interval

Proportion of patients, n/N (%)	Continued DMF[a]	New to DMF[a]	
	BID/BID	PBO/BID	GA/BID
Year 0-1 (DEFINE/CONFIRM Year 1)	95/208 (46)	30/98 (31)	14/46 (30)
Year 1-2 (DEFINE/CONFIRM Year 2)	131/204 (64)	29/85 (34)	18/44 (41)
Year 2-3 (ENDORSE Year 1)	120/188 (64)	29/68 (43)	19/39 (49)
Year 3-4 (ENDORSE Year 2)	123/179 (69)	45/63 (71)	21/36 (58)
Year 4-5 (ENDORSE Year 3)	95/152 (63)	38/56 (68)	18/29 (62)

[a]DMF, delayed-release DMF (also known as gastro-resistant DMF).

Conclusion: Reduced frequency of new MRI lesions was maintained throughout 5 years with continued DMF therapy. After switching to DMF, patients demonstrated MRI outcomes similar to those observed with DMF in DEFINE/CONFIRM. These findings, together with clinical efficacy and acceptable safety profile, support DMF as a valuable long-term treatment option for patients with RRMS.

Disclosure: Study supported by: Biogen Idec

MS and related disorders 2

P1166

Adiponectin and not leptin is associated with genetic susceptibility to multiple sclerosis

E. Kantorova[1], D. Cierny[2], P. Petrova[3], P. Slezak[4], J. Michalik[5], T. Adam[3], S. Sivak[1], V. Nosal[6], E. Kurca[7]
[1]Martin, Slovakia, [2]Jessenius Faculty of Medicine, Comenius University Bratislava, Institute of Medical Biochemistry, Martin, Slovakia, [3]Faculty Hospital in Olomouc, Czech Republic, Department of Clinical Biochemistry, Olomouc, Slovakia, [4]Comenius University, Bratislava, Department of simulation and virtual medical education, Bratislava, Slovakia, [5]Neurology Clinic and Jessenius medical faculty, Comenius university, Martin, Slovak republic, Neurology, Martin, Slovakia, [6]Jessenius Faculty of Medicine, Comenius University Bratislava, Neurology, Martin, Slovakia, [7]Jessenius Faculty of Medicine, Comenius University Bratislava, Neurology, martin, Slovakia

Background and aims: Multiple sclerosis (MS) is an inflammatory-autoimmune demyelinating disease of the CNS affecting genetically susceptible individuals. Genetic susceptibility interacts with environmental factors. A role of adipose tissue and adipokines as environmental factors of MS should be clarified.

Methods or Materials or Case Report: We investigated a potential relationship between adipokinese, adipose-tissue and HLA antigen DRB1 (single nucleotid polymorphism rs 3135388), specific markers of genetic susceptibility to MS. Total of 74 pacients MS completed the study. Patients with RR and SP forms were included. The mean age was 40.8±10.5, disease duration 11.1±4.8. Rate of disability was 3.7±1.4 (range 0-10), measured by EDSS. Adipose-tissue mass was assessed by BMI, mean value was 25.3±5.6. Leptin and adiponectin were tested by ELISA method. Statistical analysis: nonparametric Kendall-tau b test, multivariant regression analysis.

Results: We found significant association of leptin with EDSS (r=0.22, p=0.006), and adiponectin with EDSS (r=-0.17, p=0.036). In multivariant regression analysis both leptin (parcial correlation 0,28, p=0.017) and adiponectin (parcial correlation -0.19, p=0.012) were found to be good BMI-dependent predictors of progression of disability. However, adiponectin, and not leptin, correlated with the carriage of HLADRB1 and rs 3135388 A (r=0.16, p=0.053) in MS patients.

Conclusion: Adipokines, released from an excessive adipose tissue, are potent modulators of inflammatory activity in MS. Adiponectin is associated with genetic susceptibility of MS.

Disclosure: Work has been supported by Project ESF ITMS kód: 26110230067.

P1167

Evaluation of the safety, efficacy and retention of mitoxantrone in Cypriot patients with primary progressive multiple sclerosis.

E. Kkolou, E. Gaglia, J. Toufexis, M. Pantzaris
The Cyprus Institute of Neurology and Genetics, Clinical Department, Nicosia, Cyprus

Background and aims: Primary Progressive Multiple Sclerosis (PPMS) is a chronic debilitating neurological disease for which no treatment is currently available. The purpose of our study was to evaluate the real life safety, efficacy and retention of Mitoxantrone (MTX) in Cypriot patients with PPMS.

Methods: 38 adult patients were studied retrospectively for 2 years. Patients were treated with 18-20mg of MTX every 3 months up to a cumulative dose of 140mg-160 mg. Our review assessed patents' EDSS progression, treatment emergent adverse events (AEs) and MTX withdrawal rates.

Results: A significant reduction in disease progression was observed after the first year of MTX treatment compared with the year before (p=0.014). Reduction in disease progression was however not sustained for the second year of treatment (p=0.374). Nevertheless, seven patients (18%) responded to MTX therapy experiencing no disease progression during the two years of treatment. 17 patients (45 %) discontinued treatment protocol: 9 (24%) within the first and 8 (21%) within the second year of treatment. Main discontinuation reasons were patients' decision / lack of efficacy (21%) and cardiovascular AEs (13%). 21 patients (55%) experienced AEs. Most frequently reported were cardiovascular AEs (16%), psychological/psychiatric AEs (13%), nausea and vomiting (13%) and hematological abnormalities (10%).

Conclusion: Overall, Mitoxantrone failed to demonstrate reduction in disease progression in patients with PPMS. Since, however, 18% of our patients remained clinically stable throughout the 2-year treatment protocol, larger studies are required to identify possible factors affecting the response of PPMS patients to MTX treatment.

Disclosure: Nothing to disclose

P1168

Evaluation of the relationship between restless legs syndrome, sleep disturbance and quality of life measures in patients with multiple sclerosis

A. Koskderelioglu, M. Gedizlioglu, O. Onder
Izmir Bozyaka Education and Research Hospital, Department of Neurology, Izmir, Turkey

Background and aims: We aimed to find out prevalence and severity of the restless legs syndrome (RLS) in patients with multiple sclerosis (MS). We examined the relationship with fatigue, quality of life (QoL) and sleep disturbance in MS patients experiencing RLS.

Methods: We recruited 183 consecutive MS patients. Restless legs syndrome is diagnosed according to the essential criteria defined by International Restless Legs Syndrome Study Group (IRLSSG). The disease severity is determined using the IRLSSG severity scale. Gender, age, disease duration, MS pattern, EDSS scores were documented. Beck Depression Inventory, Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and MS Quality of Life-54 (MSQoL-54) questionnaires were applied to the patients.

Results: Of the 183 patients 154 (84.5%) had relapsing-remitting, 21 (11.5%) secondary progressive and 8 (4.4%) primary progressive MS. Mean age was 40.95±1.09, disease duration 9.43±6.22 years and EDSS scores 2.1±1.74. 43 patients (23.5%) were diagnosed with RLS. Statistical analysis showed a strong association with poor sleep, decreased quality of life, increased fatigue and depressive mood (p=0.004, p=0.002, p=0.003, p=0.002 respectively). The scores of FSS, physical composite scores of the MS-QoL-54 and PSQI had significant correlation with RLS severity (p=0.045, p=-0.038, p=0.001 respectively).

Conclusion: Comorbid RLS exerts a remarkable negative impact on fatigue, sleep quality, mood and QoL in MS patients. Awareness of RLS among MS patients and early treatment may contribute to an improvement in their quality of life.

Disclosure: Nothing to disclose

P1169

Lebanese Multiple Sclerosis Registry (OLSEP): first report

S. Koussa[1], A. Awada[1], H. Abboud[1], J. Hatem[1], H. Korri[1], K. Abou-Khaled[1], J. Helou[1], M. Thibault[2], A. Tourbah[3]
[1]Hotel Dieu de France Hospital, Neurology, Beirut, Lebanon, [2]CHU de Dijon, Neurology, Dijon, France, [3]Rheims, France

Background and aims: Following the guidelines of management of MS in Lebanon, an "observatoire" of MS in Lebanon was initiated in November 2012. Aims are to report the preliminary results of the Lebanese registry "OLSEP". The long-term objectives are to follow-up patients, report the effect of DMD on long term disability and follow-up on the efficacy and safety of new treatments

Methods: Data of patients with MS in Lebanon were collected between November 2012 and April 2013. Descriptive statistics are reported.

Results: Patients: 282 patients with MS were included in the observation. Sex ratio F/M is 2.42. A history of familial MS was reported in 11.7% of cases. Geographical origin: 29.45% of patients are originated from Mount Lebanon, 21.56% from South Lebanon,18.4% from Beirut, 16.56% from Bekaa and 15.33% from North Lebanon. Nearly 45% of patients are unemployed and one out of three is not married. Concerning environmental factors, one third are smokers and the level of Vitamin D is <20ng/ml in 50% of patients. Mean age of first symptoms was 31.04 years, most frequently monofocal, with sensitive symptoms, and involving the spinal cord. Patients were most often in a RR phase of the disease, and 2/3 patients had an EDSS <3.5. Fatigue was reported in 48% of patients

Conclusion: The preliminary descriptive data of the OLSEP in Lebanon shows results that are comparable to other registries. Myelitis is predominant as presenting syndrome, and vitamin D levels are low in nearly half of the evaluated patients

Disclosure: Nothing to disclose

P1170

Safety, tolerability, and immunogenicity of peginterferon Beta-1a: combined analyses of the Phase III ADVANCE study and interim analysis from the extension study ATTAIN

M. Kremenchutzky[1], J. White[2], S. Liu[2], Y. Cui[2], S. Hung[2], A. Seddighzadeh[2], V. Evilevitch[2], G. Sabatella[2]
[1]Western University , London, Canada, [2]Biogen Idec Inc., Cambridge, USA

Background and aims: ATTAIN is a 2-year extension study of ADVANCE; the following analysis examines subcutaneous peginterferon beta-1a (PEG-IFN) safety, tolerability, and immunogenicity in relapsing-remitting multiple sclerosis (RRMS) patients up to the ATTAIN Year 1 interim cutoff (August 1 2014).

Design/methods: Patients aged 18–65 were assigned to either PEG-IFN dosed every 2 or 4 weeks, or delayed treatment (placebo for Year 1 followed by PEG-IFN every 2 or 4 weeks for subsequent years). Delayed treatment patients were included in appropriate analysis groups based on Year 2 dosing. All patients are in the process of transitioning to every 2 week dosing in accordance with approved labels (post-interim cut-off).

Results: At cutoff, mean time of drug exposure was 127.0 weeks (range: 2-224). Over all years of treatment in ADVANCE and ATTAIN, incidence of adverse events (AEs) were 96% (n=710/740) and 96% (n=697/728), and incidence of serious AEs (including relapses) were 21% (n=157/740) and 28% (n=202/728), every 2 and 4 weeks, respectively. Incidence of discontinuations due to AEs were 8% (n=62/740) and 7% (n=54/728) every 2 and 4 weeks, respectively. Incidence of persistent antibodies over all years of treatment in ADVANCE and ATTAIN were: interferon-binding antibodies: 6% (42/706) and 4% (25/706), interferon-neutralizing antibodies: <1% (n=6/715) and <1% (n=2/716), and anti-PEG antibodies: 3% (n=20/681) and 5% (n=37/682), every 2 weeks and every 4 weeks, respectively.

Conclusion: In RRMS patients, long-term safety and tolerability of PEG-IFN remains favorable (without previously unseen events recorded), and development of persistent neutralizing antibodies over all years is very low.

Disclosure: This study has been sponsored by Biogen Idec Inc. (Cambridge, MA, USA).

P1171

Ability of clinical and visual perceptive computing motor assessments to reflect daily activity in patients with multiple sclerosis

T. Krüger[1], K. Otte[2], B. Kayser[2], S. Mansow-Model[2], A. Grobelny[1], E. Gusho[1], T. Schmitz-Hübsch[3], F. Paul[4], A. Brandt[5], J. Behrens[1]
[1]Charité – University Medicine Berlin, NeuroCure Clinical Research Center, Berlin, Germany, [2]Motognosis UG (haftungsbeschränkt), Berlin, Germany, [3]Charité, Department of Neurology, Berlin, Germany, [4]Charité, NeuroCure Clinical Research Center and Department of Neurology, Berlin, Germany, [5]Motognosis UG (haftungsbeschränkt) and Charité, NeuroCure Clinical Research Center, Berlin, Germany

Background and aims: In clinical care and research, clinical assessments should reflect changes in patients' quality-of-life. Patients with multiple sclerosis (MS) experience motor impairment, reducing physical activity and negatively impacting patients' everyday life. Motor impairment is routinely assessed by expanded disability status scale (EDSS) and the Timed 25-Foot Walk Test (T25FW). Gait and stance tests using perceptive computing based on Microsoft's Kinect promise reliable and rater-independent assessments. Objective of the on-going study is to investigate to which extent different clinical assessments reflect MS patients' daily activity.

Methods: Daily activity of 20 MS patients and 20 matched controls is measured using SenseWear activity monitors (SAM) for a 7-day-period and expressed as the mean moderate-to-vigorous-physical-activity in min/day (MVPA) from the SMA's recordings from all days. Motor impairment is assessed using EDSS, T25FW as well as Kinect-based short maximum speed walk (SMSW) and postural control (POCO). Patient questionnaires include the 12-Item MS Walking Scale (Walk-12).

Results: Wearing of SAM was well tolerated and recorded data of good quality. Preliminary data analysis from 6 patients showed that MVPA showed a mild correlation with rater-dependent EDSS scores (unsigned (u) Spearman's Rho=0.35), but good to excellent correlation with objective assessments T25FW, SMSW and POCO (all uRho >0.75). Correlation with self-reported walking disability (Walk-12) was moderate (uRho=0.6).

Conclusion: Commonly used clinical motor assessments reflect daily activity in MS patients. Objective tests show a higher association with daily activity than subjective tests and questionnaires. Final analysis will include associations with regard to detailed factors of daily activity.

Disclosure: This study is partly funded by Novartis Pharma GmbH Arzneimittel, Carmerstraße 18, 10623 Berlin.

P1172

Interleukine 17 is not detected in active MS patients' sera but in CSF in radiologically and clinically isolated syndromes

C. Lebrun Frenay[1], M. Cohen[1], F. Bucciarelli[2], B. Seitz-Polzi[3], A. Cornille[3], B. Pignolet[4], S. Benzaken[3], D. Brassat[5]

[1]Pasteur, Nice, France, [2]Purpan, Toulouse, France, [3]Archet, Nice, France, [4]inserm, Toulouse, France, [5]Hopital PPR - CHU Purpan, Neurology, Toulouse, France

Background and aims: Increased serum IL-17 levels are associated with numerous autoimmune diseases. In MS, exploratory studies reported increased levels in CSF but results in detecting IL-17 in serum are controversied, sometimes detected during relapses or in case of IFNbeta non response.

We investigate levels of IL-17 in serum and CSF in patients diagnosed as Radiologically Isolated syndrome, Clinically Isolated Syndrome or active multiple sclerosis patients (RIS, CIS, A MS) as a marker of inflammatory condition.

Methods: 1177 patients with active MS, defined by 2 recent relapses and gadolinium enhancing lesions, 35 patients diagnosed with RIS, 35 with CIS.The cytokine IL-17 A was measured in Serum and CSF using a FIDIS Human cytokine IL17 kit.

Results: IL-17A was not detected in blood samples neither in AMS nor in RIS or CIS patients excepted for 25 AMS patients with a mean of 0.52 pg/ml (0.09-1.33). The detection rate of IL-17 A was strictly identical in the CSF of RIS or CIS patients, respectively 0.70 pg/ml (0.31-1.46) and 0.72 pg/ml (0.31-1.46). No correlation was found between CSF IL level and number of Barkhof Criteria on the initial brain MRI, detection of brain or spinal gadolinium enhancing lesions, presence of spinal cord lesions,CSF increased IgG Index or detection of oligoclonal band.

Conclusion: These findings strongly suggest that in RIS and in CIS patients, intrathecal activation of the IL-17 is similar, confirming that RIS is the initial step of the demyelinating disease.

Disclosure: On behalf CFSEP, BIONAT and BEST MS groups B Pignolet and F Bucciarelli received grants NCT00942214 and NCT01981161

P1173

Colesevelam HCl for accelerated elimination of teriflunomide, and monitoring of teriflunomide concentration using dried blood spot assay

C. Lunven[1], Z. Guo[2], A. Filali-Ansary[1], S. Turpault[2], A. Delfolie[1], N. Boyanova[3], N. Fauchoux[4]

[1]Sanofi R&D, Chilly-Mazarin, France, [2]Sanofi US, Bridgewater, USA, [3]Genzyme, a Sanofi company, Cambridge, USA, [4]Biotrial, Rennes, France

Background and aims: Teriflunomide is a once-daily oral immunomodulator approved for treatment of relapsing-remitting MS. In cases of emerging toxicity, overdose, or pregnancy, elimination of teriflunomide can be accelerated by oral administration of cholestyramine. Compared with cholestyramine, colesevelam HCl may offer improved tolerability for patients. We report an open-label study to assess the effectiveness of colesevelam HCl for accelerated elimination of teriflunomide. Teriflunomide concentrations were assessed in parallel in plasma and dried blood spot (DBS) samples.

Methods: Healthy subjects aged 18–45 years received teriflunomide 70mg once daily for 5 days, followed by an 11-day accelerated elimination procedure (AEP) of colesevelam HCl (4.375g total daily dose, 4 x 625mg + 3 x 625mg). If plasma teriflunomide concentration was >0.02µg/mL at AEP end, subjects received precautionary cholestyramine 4g tid until it was ≤0.02µg/mL. Teriflunomide concentrations were determined in plasma and finger-prick DBS. Safety and tolerability were also evaluated.

Results: In the 18 subjects enrolled, mean (standard deviation) plasma teriflunomide concentration was 36.3(6.42)µg/mL at AEP start, and 1.33(0.833)µg/mL after the 11-day AEP; a 96.1% decrease. All subjects received cholestyramine to eliminate residual teriflunomide. Finger-prick DBS concentrations were correlated with plasma concentrations (R-squared=0.97); DBS methodology was selective, repeatable, and reproducible. The drugs were well tolerated; no unexpected safety signals emerged.

Conclusion: Colesevelam HCl administration accelerated teriflunomide elimination, with a 96% decrease in plasma teriflunomide concentration after 11 days. Correlation between plasma and finger-prick DBS concentrations was demonstrated. Together, these findings may provide additional options for monitoring teriflunomide concentration and for accelerated elimination of teriflunomide in the real-world setting.

Disclosure: Study supported by Genzyme, a Sanofi company.

P1174

Evaluation of relapses as a surrogate marker for confirmed disability progression in relapsing-remitting multiple sclerosis patients treated with peginterferon beta-1a using the Prentice criteria

X. You[1], T. Scott[2], S. Shang[1], B. Sperling[1]
[1]Biogen Idec Inc., Cambridge, USA, [2]Allegheny General Hospital, Department of Neurology , Pittsburgh, USA

Background and aims: It is not known whether the treatment effect of subcutaneous peginterferon beta-1a (PEG-IFN) on confirmed disability progression (CDP) in relapsing-remitting multiple sclerosis patients in the Phase III ADVANCE study was fully driven by its effect on relapses. Using the Prentice criteria, we evaluated whether relapses could serve as a surrogate marker for CDP for the treatment effect of PEG-IFN every 2 weeks versus placebo over 1 year in the ADVANCE study, and for the treatment effect of intramuscular interferon beta-1a once weekly versus placebo over 2 years in the MSCRG study.

Methods : The four Prentice criteria are: 1. treatment effect is significant for S; 2. treatment effect is significant for T; 3. T is significantly correlated with S; 4. treatment effect on T can be fully explained by S, where T is the "true" outcome (24-week CDP) and S is the surrogate marker (relapses). For S to qualify as a surrogate marker for T, all four Prentice criteria must be met according to the corresponding p-values.

Results: In the ADVANCE study, the first three Prentice criteria were met. However, criterion 4 failed because treatment effect on CDP is still significant (coefficient for treatment effect=-0.6126, p=0.0323) after adjusting for relapses. In the MSCRG study, all four criteria were met.

Conclusion: Relapses qualify as a surrogate marker for 24-week CDP in the MSCRG study for intramuscular interferon beta-1a but not in the ADVANCE study for PEG-IFN, implying that PEG-IFN might have an additional effect on CDP beyond its effect on relapses.

Disclosure: This study has been sponsored by Biogen Idec Inc. (Cambridge, MA, USA).

Neurogenetics 1

P1175
Progressive aphasia, cortical blindness and cortical deafness in MELAS syndrome

P. Pérez Torre, A. Escobar Villalba, F. Acebrón, R. Álvarez Velasco, P. Agüero Rabes, N. García Barragán, J. Buisán Catevilla, I. Corral Corral
Hospital Ramón y Cajal, Madrid, Spain

Background and aims: MELAS syndrome (myopathy, encephalopathy, lactic acidosis and stroke-like episodes) frequently presents cortical disorders. Acute progressive bilateral involvement of temporo-parieto-occipital cortex is rare. We report a patient with MELAS syndrome who suffered a progressive episode with hemianopsia, aphasia, cortical blindness and cortical deafness.

Case Report: A 30-year-old male patient, with no relevant family history, was admitted with left homonymous hemianopsia. Eighteen months before he had repeated seizures for which he was receiving levetiracetam. Two weeks after admission rapidly progressive neurological worsening developed in four days, with memory deficits, predominantly sensory aphasia, cortical blindness, cortical deafness and seizures. The patient was aggressive and could contact only by touch. Serial magnetic resonance imaging showed progressive extensive bilateral lesions involving temporo-parieto-occipital cortex, with mild edema. Lesions were hyperintense in T2-weighted sequences and showed restriction in diffusion sequences.

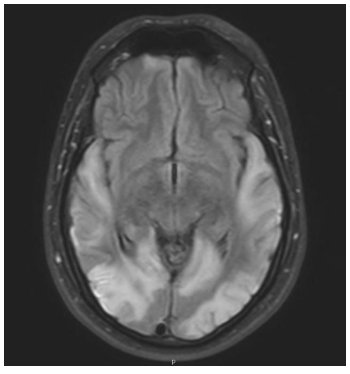


Image 1 (axial). Hyperintense lesions in Flair-Spair sequences involving temporo-occipital cortex.

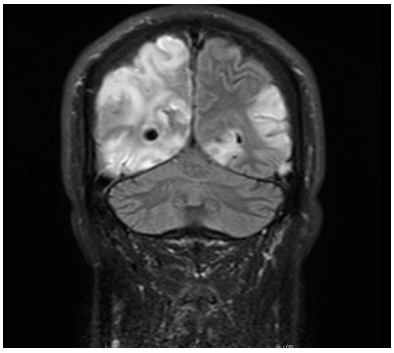


Image 2 (coronal). Hyperintense lesions in Flair-Spair sequences involving temporo-parietal cortex.

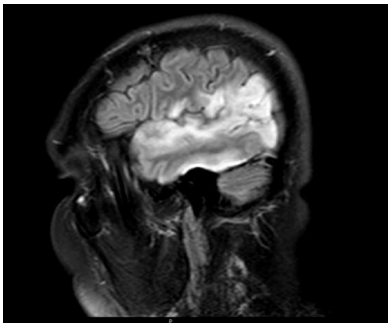


Image 3 (sagital). Hyperintense lesions in Flair-Spair sequences involving temporo-parieto-occipital cortex.

Results: Analysis showed high lactate levels in blood and cerebrospinal fluid. A muscle biopsy showed no myopathy or ragged red fibers. The genetic study confirmed a MELAS mutation at the base pair 3243A-G. Empirical treatment with coenzyme Q and vitamin complexes resulted in significant improvement after 3 months.

Conclusion: MELAS syndrome should be considered in young adults with progressive cortical lesions despite normal muscle biopsy.

Disclosure: Nothing to disclose

P1176
Abstract cancelled

P1177

ANO10 mutation causing an autosomal recessive cerebellar ataxia in two siblings

D. Rudd[1], S. Omer[2], M. McEntagart[3]
[1]Tooting, [2]St George's Hospital, Neurology, [3]St George's Hospital, Clinical Genetics, London, United Kingdom

Background and aims: Autosomal recessive cerebellar ataxias are a clinically diverse group of conditions. Despite recent advances in gene sequencing techniques, approximately half of patients do not receive a molecular diagnosis.

Methods: We report the cases of two siblings with a cerebellar syndrome characterised by progressive ataxia, nystagmus and dysarthria with onset of symptoms in the third decade of life. In both cases marked cerebellar atrophy was noted on Magnetic Resonance Imaging (MRI). Molecular genetic testing revealed that both individuals were compound heterozygous for two pathogenic variants in Anoctamin 10 (ANO10), predicted to lead to premature termination of gene translation.

Results: A genetic panel comprising 57 genes for hereditary ataxia was performed. Sanger sequencing revealed two pathogenic ANO10 variants; c132dupAp.(Asp45fs) and c96delAp.(Glu33fs).

Conclusion: ANO10, also known as TMEM16K, is postulated to encode a calcium activated chloride channel, with highest expression within the adult brain and retina. Mutations in ANO10 have been reported in only five families worldwide. The phenotype encompasses cerebellar ataxia, dysarthria, eye movement abnormalities and severe cerebellar atrophy, with variable additional features of cognitive impairment, motor neurone involvement, seizures and retinal degeneration. More recently, ANO10 mutations have been associated in two patients with deficiencies in Coenzyme Q10, with supplementation leading to a mild improvement in the clinical symptoms. Our case report helps further define the clinical spectrum of this rare condition.

Disclosure: Nothing to disclose

P1178

Abstract cancelled

P1179

Investigation of four vitamin D receptor (VDR) gene polymorphisms in sporadic amyotrophic lateral sclerosis

N. Török[1], R. Török[2], P. Klivényi[2], J. Engelhardt[2], L. Vécsei[1]
[1]Szeged, Hungary, [2]University of Szeged, Department of Neurology, Szeged, Hungary

Background: There are aberrations in vitamin D–endocrine system in sporadic amyotrophic lateral sclerosis (SALS). Vitamin D deficiency and the rise of the levels of calcium and parathormon were measured in the sera of ALS patients. Diverse proteins were identified which link vitamin D to the theories of the selective degeneration of motor neurons too, albeit alterations of the VDR gene have not been reported.

Objective: Our aim was to investigate the single nucleotide polymorphisms of VDR gene in SALS patients in Hungary.

Methods: 77 SALS patients and 98 healthy controls were enrolled to reveal the supposed different proportion of the alleles of the VDR receptor. Restriction fragment length polymorphism was used. For data analysis, SPSS software 20.0 was utilized.

Results: One of the investigated SNPs (ApaI CC genotype) was significantly lower (p=0.002) in the group of ALS patients than in controls. The age at onset of the disease of the patients carrying this or the other alleles were not significantly different.

Conclusion: One of the four examined polymorphisms of the VDR gene (ApaI CC genotype) seems to be protective from SALS in Hungarian population. However, due to the low number of cases, another study from the Central European region is needed. Our previous results suggest that the effect of Vitamin D may inhibit the local CNS inflammation and induce the synthesis of calcium-binding proteins in motor neurons. To our knowledge, this is the first described SNP in the literature which may have protective effect in this devastating disease.

Disclosure: Nothing to disclose

P1180

Oculodentodigital dysplasia with massive brain calcifications and a new pathogenic mutation

G. Tumminelli[1], I. Di Donato[1], A. Rufa[1], A. De Luca[2], S. Salvatore[1], M. Di Giovanni[1], A. Federico[1]

[1]University of Siena, Neurology and Neurometabolic Diseases Unit, Department of Medicine, Surgery and Neuroscience, Sienna, Italy, [2]IRCCSCSS, San Giovanni Rotondo e Istituto CSS-Mendel, Rome, Italy

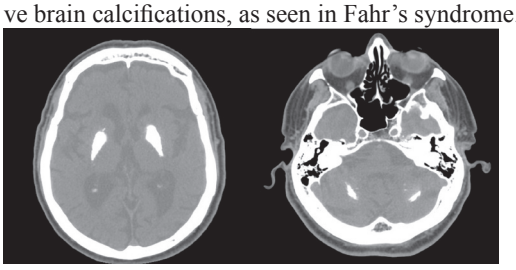
Background and aims: Oculodentodigital dysplasia (ODDD) [MIM 164200] is a rare autosomal dominant disorder caused by mutations in the gap junction alpha 1 (GJA1) gene, on chromosome 6, encoding for connexin 43. Typical signs include type III syndactyly of the fourth and fifth finger, microphtalmia, microcornea, short palpebral fissures, microdontia, enamel hypoplasia and neurological disturbances (spastic paraparesis, ataxia, neurogenic bladder dysfunction and occasionally mental retardation).

Case Report: We report a 59-year-old man, observed for progressive gait disturbances and unsteadiness. presenting since birth bilateral type III syndactyly of the third, fourth and fifth finger (surgically corrected) and bilateral syndactyly of second and third toe. Decreased visual acuity with glaucoma and cataracts, microdontia, caries and teeth loss were evident since childhood. Clinical examination showed the classical ODDD features. Neurologically, blindness, unsteady and spastic gait, spasticity of inferior limbs were present. A CT scan revealed gross calcifications of basal ganglia and cerebellar nuclei bilaterally. MRI showed thin corpus callosum and mildly enlarged ventricles. P and Ca metabolism examination, including PTH, was normal.

Classical ODDD features in our patient

Results: The clinical findings suggested ODDD, with some atypical features rarely reported (massive brain calcifications). Molecular genetic analysis of the GJA1 gene revealed a heterozygous missense mutation (NM_000165.3:c.124G>C;p.Glu42Gln) never previously reported which, according to bioinformatical studies, resulted pathogenic

Conclusion: In conclusion, this case expands the knowledge of the ODDD syndrome, with the evidence of a new mutation of connexin 43 gene and the possibility that this gene may also alter the brain microvessels leading to massive brain calcifications, as seen in Fahr's syndrome.



Gross calcifications in basal ganglia and cerebellar nuclei

Disclosure: Nothing to disclose

P1181

The implementation of the next generation sequencing (NGS) to identify the genetic background of the autism spectrum disorder (ASD) in Hungarian patients

N.A. Varga[1], K. Pentelényi[1], P. Balicza[1], V. Hársfalvi[1], V. Reményi[1], J. Koller[1], C. Prekop[2], S. Magyarósi[1], M.J. Molnár[1]

[1]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Neurology, Budapest, Hungary, [2]Vadaskert Kórház és Szakambulancia, Budapest, Hungary

Background and aims: The genetic background of ASD is highly heterogeneous. The first step is to distinct the monogenic forms from complex, multifactorial forms.
Our aim is to explore the effectivity of NGS in the screening of syndromic-monogenic forms in our Hungarian ASD cohort, and to estimate the frequency of mutations in the genes related to ASD.

Methods: Our cohort consisted of 47 patients. We performed NGS on MiSeq platform targeted on 103 known and candidate genes related to ASD (Illumina Trusight Autism). Before the NGS the FMR1 gene were screened out by Asuragen AmplideX PCR Kit.

Results: The genetic analysis detected in 45 patients rare variants in 39 genes. Phenotypically 29 patients were considered as idiopathic ASD patient, 18 had an additional feature beside autism. In 2 patients we detected FMR1 full mutation. In 1 case the ASD associated to muscular dystrophy, the NGS detected point mutations in the dystrophin genes. In a boy presenting symptoms of CHARGE syndrome, a CHD7 frameshift mutation confirmed the diagnosis. In case of a boy profoundly affected, with multifocal epilepsy, the CDKL5 missense mutation is supposed to be pathogenic on the bases of a similar case. In the most cases pathogenic SNPs were found in CDH8, LAMC3, MET, NLGN3, SHANK2, SHANK3, VPS13A genes supporting their strong predisposing effect on the ASD. In these cases the segregation analysis of the families are going on.

Conclusion: The identification of the monogenic forms is extremely important because only in this case we can determine the reoccurrence risk and can offer prenatal testing.

Disclosure: The project is supported by the Hungarian Government, financed by the Research and Technology Innovation Fund. KTIA_AIK_12-1-2013-0017

P1182

Friedreich's ataxia in Norway

I.M. Wedding[1], S.P. Henriksen[2], M. Kroken[3], T. Berge[2], T. Fiskerstrand[4], K.K. Selmer[3], C. Tallaksen[1]

[1]Oslo, Norway, [2]Oslo University Hospital, Research Unit for Neuroscience, Oslo, Norway, [3]Oslo University Hospital, Department of Medical Genetics, Oslo, Norway, [4]Haukeland University Hospital, Department of Medical Genetics, Bergen, Norway

Background and aims: Friedreich's ataxia (FRDA) is an autosomal recessive hereditary ataxia, due to degeneration of the dorsal root ganglia and dorsal medulla. It is described as the most common hereditary ataxia in Caucasians, with an estimated prevalence of 1/50000 and a carrier frequency up to 1/60 in Europe. In 95-98% of the cases homozygous GAA repeat expansions in the FXN-gene lead to reduced levels of the mitochondrial protein Frataxin. FRDA expected to be rare in Norway compared to Europe. Previous prevalence studies show variations from of 1/100 000 (1974) in Western Norway to 1/1350000 in the South-Eastern part of Norway (2008). The aims of this project was to assess the prevalence and carrier frequency of FRDA in the whole of Norway. In addition, we wanted to give a thorough clinical and molecular characterisation of the Norwegian FRDA patients and healthy carriers, including GAA repeat expansion sizes and frataxin levels.

Methods: Patients were collected through nation-wide hospital archive searches and examined clinically. Carrier frequency, GAA repeat expansion size and frataxin protein levels were analyzed with previously described methods.

Results: 29 genetically confirmed FRDA patients were found, corresponding to a total prevalence of 1/176 000 in Norway. Among ethnic Norwegians the prevalence was 1/191 000. The carrier frequency among ethnic Norwegians is 1/210.

Conclusion: In this first comprehensive study of FRDA in Scandinavia, the prevalence and carrier frequency of FRDA in Norway is lower than in Central Europe, but higher than previously described in Norway.

Disclosure: Nothing to disclose

P1183

Application of whole exome sequencing to study a cohort of Greek patients with heterogeneous neurological disorders

H. Latsoudis[1], E. Vogiatzi[1], A. Evangeliou[2], V. Mastorodemos[1], D. Kotzamani[1], K. Monti[2], D. Zafeiriou[2], G. Amoiridis[1], A. Plaitakis[1], I. Zaganas[1]

[1]University of Crete, Neurology, Heraklion, Crete, Greece, [2]Aristotle University of Thessaloniki, Pediatrics, Thessaloniki, Greece

Background and aims: Next generation sequencing methodologies, including whole exome sequencing (WES), are gaining grounds in the investigation of neurological diseases. In this study, we aimed to evaluate the diagnostic efficacy of WES in a cohort of Greek patients with various neurological syndromes.

Methods: Patients presenting to study clinicians with neurological syndromes suspected to be genetic in origin were offered WES, on the basis of predefined criteria. After obtaining informed consent, WES was performed on 27 patients (14 females and 13 males; mean age=23.4±23.8yrs, range 2-71yrs) in a CLIA certified laboratory, aiming at a 50X coverage. Data analyses were performed in the Neurology Laboratory, University of Crete, Greece, by integrating clinical information with published phenotypic data. Findings were verified by Sanger sequencing.

Results: The overall diagnostic rate of WES was 44.4% (12/27 patients). Specifically, causal variants were identified in the following genes: NF1 (Neurofibromatosis type I), EPM2A (Lafora disease), CLCN1 (congenital myotonia), CAPN3 (muscular dystrophy), ISPD (muscular dystrophy), TARDBP (ALS/FTLD), PAX6 (nystagmus/aniridia syndrome), NIPBL (Cornelia de Lange syndrome), GAA (Pompe disease), CPT2 (rhabdomyolysis), ALDOB (hereditary fructose intolerance) and PDHX (lactic acidosis). In 2 cases (NF1, CLCN1), WES was chosen over targeted sequencing due to lower cost. In the remaining 10 cases, WES provided final diagnosis after several costly and laborious diagnostic tests were inconclusive.

Conclusion: In our cohort of selected neurologic patients, WES showed high diagnostic yield and was cost effective. These data offer support to the value of WES to resolve the diagnostic odyssey of patients with heterogeneous neurogenetic disorders.

Disclosure: Nothing to disclose

Peripheral nerve disorders 1

P1184

Red-flag symptom clusters in transthyretin familial amyloid polyneuropathy (TTR-FAP)

I. Conceicao[1], A. González Duarte[2], L. Obici[3], H. Schmidt[4], D. Simoneau[5], M.-L. Ong[6], L. Amass[7]

[1]CHLN, Hospital de Santa Maria and Clinical and Translational Physiology Unit, Physiology Institute, Faculty of Medicine, IMM, Lisbon, Portugal, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico, [3]Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [4]Universitätsklinikum Münster, Münster, Germany, [5]Pfizer Inc., Paris, France, [6]Pfizer Inc., New York/NY, USA, [7]Pfizer Inc., Collegeville/PA, USA

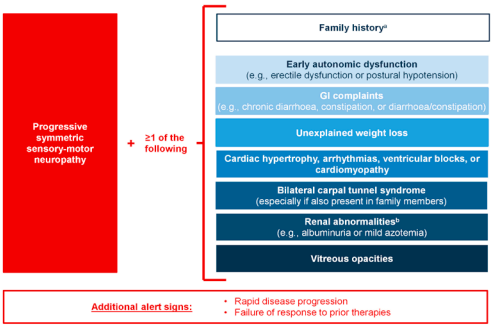
Background: TTR-FAP is a progressive, fatal, autosomal-dominant disorder characterised by extracellular deposition of transthyretin-derived amyloid fibrils in various organs, particularly peripheral and autonomic nerves, heart, gastrointestinal tract, kidneys, eyes, and connective tissue of the transverse carpal ligament. Due to its phenotypic variability and non-specificity of symptoms, the condition can be difficult to recognise and manage. Misdiagnosis is common and definitive diagnosis can be delayed for years, postponing adequate management and genetic counselling and leading to possible irreversible damage.

Objective: To improve disease awareness and provide a practical guide when to suspect TTR-FAP with the goal to shorten time to diagnosis.

Methods: Considering all known characteristics and manifestations of TTR-FAP, combinations of red-flag signs and symptoms that should arouse suspicion of TTR-FAP were identified. Selection was guided by relevant published literature, common misdiagnoses, and the authors' expert clinical experience in diagnosing and treating patients with TTR-FAP.

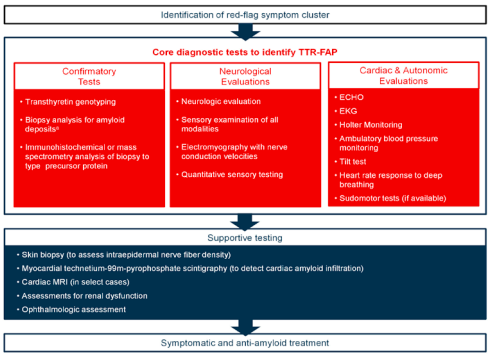
Results: See Figures 1 and 2.

Figure 1. Potential red-flag symptom clusters that may warn of a diagnosis of TTR-FAP.



[a] More than one family member known or suspected to be affected by TTR amyloidosis or with feature(s) suggestive of the condition (e.g., neuropathy, wasting syndrome, non-ischemic cardiomyopathy, or sudden death at young age).
[b] Renal impairment may be associated with only some pathogenic TTR mutations.

Figure 2. Diagnostic approach upon identification of red-flag symptom clusters in patients with no family history.



[a] A negative finding does not exclude a diagnosis of TTR amyloidosis.

Conclusion: TTR-FAP should be suspected if progressive peripheral polyneuropathy and one (or a combination) of the following symptoms are observed: early autonomic dysfunction, cardiac involvement, severe chronic diarrhoea, constipation, or alternating bouts of constipation and diarrhoea, inexplicable weight loss, carpal tunnel syndrome, renal impairment, or vitreous opacity. Common misdiagnoses include chronic inflammatory demyelinating polyneuropathy (CIDP), progressive diabetic neuropathy, and paraneoplastic syndrome. Family history should be investigated and a small-fibre assessment, nerve conduction studies, electro- and echocardiogram, laboratory evaluations, transthyretin genotyping and tissue biopsy should be performed. Early diagnosis is key to effective patient management and prevention of disease progression.

Disclosure: Funded by Pfizer Inc.

P1185

Cutaneous silent period in the assessment of small nerve fibres of peripheral nerves in lower limbs in patients with diabetes

A. Khuraibet[1], H. Rashad[1], R. Rouseff[1], R. Zorec[1], J. Ravnik[1], J. Al-Hashel[2], H. Al-Baghli[1], M. Denislic[1]

[1]Ibn Sina Hospital, Department of Clinical Neurophysiology, Kuwait, Kuwait, [2]Ibn Sina Hospital, Department of Clinical Neurology, Kuwait, Kuwait

Background and aims: The prevalence of neuropathy in patients with diabetes is about 30% and approximately 50% of patients may develop polyneuropathy during the course of metabolic disease. Routine electrophysiological examination reflects the function of large, but not the function of small nerve fibres. The purpose of our study was to evaluate the function of small nerve fibres measuring cutaneous silent period (CSP) of the peripheral nerves on lower limbs.

Methods: The evaluation of large diameter nerve fibres was performed by standard neurophysiological examination, CSP by stimulation of the sural nerve and detection over tibialis anterior muscle. The onset latency was recorded at the beginning of voluntary muscle activity suppression and the late latency at the start of new muscle activity. The difference between the latencies reflects the duration of CSP.

Results: In our study we included 20 diabetic patients (mean age 56.2±12.3 years) with mean duration of diabetes 11.90±10.2 years. The nerve conduction parameters and CSP values were compared with the corresponding parameters of the control group (47 subjects). The onset latency L1 was prolonged in half of the diabetic patients. The duration of CSP in patients (Figure 1) was significantly shorter - mean 41.08±14.80 ms vs. 57.64±13.84 ms in the control group ($p<0.005$). The peroneal and tibial motor velocities in the patients group were decreased ($p<0.001$) and H-reflex latencies prolonged ($p<0.005$).

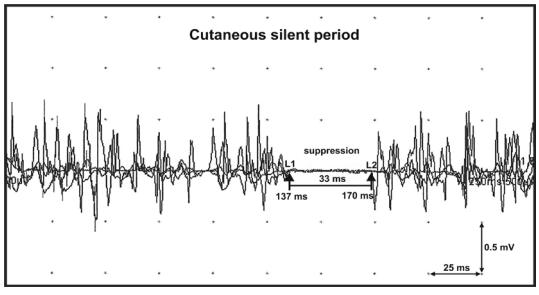


Figure. Cutaneous silent period.

Conclusion: CSP is a useful method in detecting the small nerve fibres involvement in diabetic patients and completing the routine electrophysiological evaluation.

Disclosure: Nothing to disclose

P1186

Prognostic factors affecting long term disability in polyneuropathy associated with antibodies to myelin associate glycoprotein (MAG)

M. Tondelli[1], A. Ariatti[1], E. Canali[2], F. Valzania[1], R.D'amico[3], S. Balduzzi[3], P. Nichelli[1], G. Galassi[1]

[1]University of Modena, Biomedical,metabolic,neural sciences, Modena, Italy, [2]Neurology Unit, S. Maria Nuova Hospital , Reggio Emilia, Italy, Reggio Emilia, Italy, [3]University of Modena, Diagnostic,clinical public health, Modena, Italy

Background and aims: Anti-MAG polyneuropathy is a progressive immune-mediated neuropathy whose disease course can be highly variable. The purpose of our study was to identify prognostic factors affecting long-term disability in a prospective cohort of 43 patients evaluated during a 15 years-long follow-up.

Methods: Clinical, demographical, and neurophysiological data were collected every 6 months, Several prognostic factors were considered including age, gender, type of treatment, serum anti-MAG IgM titer, serum IgM protein level at baseline, and electrophysiological pattern. Outcome measures were worsening of muscle strength, disability, sensory function, and development of hematologic malignancy.

Results: Median age at first visit was 70 years, median anti-MAG IgM titer at baseline was 20.61 BTU. Electrophysiological assessment was consistent with a pure demyelinating polineuropathy in 17.07%; the remaining 82.93% showed axonal or mixed pattern. Disability, muscle strength, and sensory function progressed and worsened significantly between the first and the last visit. No statistical significant change was observed in quality of life. Survival analyses showed that factors influencing disability were therapy (longer stability in treated patients, p=0,026), electrophysiological pattern (longer stability in axonal or mixed forms, p=0,030), and age (longer stability in younger patients, p=0.045). Older age (≥70 years) was also associated with higher risk of sensory function worsening (p=0.05). No statistical significant prognostic factors were detected for muscle strength outcome, haematology malignancy, and quality of life.

Conclusion: Our results suggest that younger age, axonal or mixed electrophysiological pattern, and therapy could be considered useful prognostic factor of decrease risk of disability in anti-MAG neuropathy.

Disclosure: Nothing to disclose

P1187

Sensory Guillain-Barré syndrome: clinical and electrophysiological features in three patients

J. Pardo Fernandez[1], T. Garcia Sobrino[1], E. Rodríguez Castro[1], M.P. Vidal Lijo[2], M.D. Montiel[3]
[1]Hospital clinico, neurology, [2]Hospital clinico, neurophysiology, [3]Servicio galego de saude, SAP de fontiñas, Santiago de Compostela, Spain

Background and aims: The rare sensory variant of Guillain-Barré Syndrome (GBS) was well defined in a series of eight patients with an acute pure sensory neuropathy (Oh et al, 2001). Only single case reports and small series meeting these criteria have been barely reported. We describe clinical and electrophysiological features of three new patients with sensory GBS.

Methods: We carried out a retrospective study of patients diagnosed with GBS in the last five years. Inclusion criteria for sensory GBS: Acute sensory neuropathy, monophasic course, arreflexia, no weakness or only minimal motor involvement and albuminocytological dissociation. Patients with an alternative diagnosis were excluded.

Results: Out of 59 patients with GBS, 3 (5%) had an acute sensory neuropathy. All 3 patients were males, with a median age of 35±17.7 years. In all of them, an infectious event was found in the previous two weeks. Distal paresthesia was the presenting symptom. Neurological examination was suggestive of an acute sensory ataxic neuropathy in patient 1, acute sensory large and small fiber neuropathy in patient 2 and acute sensory small-fiber neuropathy in patient 3. Arreflexia and albuminocytological dissociation were present in all three patients. Sensory conduction studies showed a pattern of an abnormal median-normal sural sensory response in patients 1 and 2 and were normal in patient 3. Serum antiganglioside antibodies were negative. 2 patients were treated with immunoglobulins and all of them experienced a complete recovery.

Conclusion: Sensory GBS includes subtypes with different clinical features and electrophysiological findings. Further studies are needed to develop a practical nosological classification.

Disclosure: Nothing to disclose

P1188

A profile of chronic demyelinating dysimmune neuropathies at a University Hospital

T. Garcia Sobrino[1], E. Costa Arpín[1], M.P. Vidal Lijo[2], E. Corredera[1], A. Sesar Ignacio[1], M. Arias Gomez[1], J.M. Prieto González[1], M. Lema Bouzas[1], J. Pardo Fernandez[1], I. Illa[3], L.A. Querol Gutierrez[4]
[1]Hospital Clínico, Servicio de Neurología, Santiago de Compostela, Spain, [2]Hospital clinico, neurophysiology, Santiago de compostela, Spain, [3]Hospital de la Santa Creu i Sant Pau, Neurology, Barcelona, Spain, [4]Barcelona, Spain

Background and aims: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and paraproteinemic demyelinating neuropathy are the main chronic demyelinating dysimmune neuropathies. We aim to study the spectrum of these neuropathies in a Tertiary University Hospital.

Methods: We carried out a retrospective study of patients diagnosed with CIDP, paraproteinemic neuropathy and MMN evaluated in our hospital in the last five years (2009-2014). Patients were included if they fulfilled the diagnostic criteria of the EFNS/PNS task force.

Results: 30 patients (50% males) with a median age at onset of symptoms of 57±17 years were studied. CIDP was the most frequent diagnosis (83%). 8 of them (32%) had an atypical CIDP, including 2 patients with Lewis-Sumner syndrome, 2 cases of pure sensory and 2 pure motor neuropathy, another patient with a focal CIDP and another case with combined central and peripheral demyelination (CCPD). MMN and distal adquired demyelinating symmetric neuropathy (DADS) were less frequent (7% and 10%). Relapsing and remitting disease was evident in 6 patients (20%). 5 patients (17%) had associated a monoclonal gammpopathy (80% IgM). Neurofascin IgG4 antibodies were evident in one patient with disabling tremor and poor response to immunoglobulins treatment. All patients with DADS neuropathy had positive antibodies against myelin-associated glycoprotein (anti-MAG).

Conclusion: Chronic demyelinating dysimmune neuropathies are heterogeneous. Typical CIDP was the most frequent type, followed by DADS neuropathy and MMN. CIDP associated with neurofascin IgG4 antibodies was only found in 1 case and no patient had anti-contactin-1 antibodies.

Disclosure: Nothing to disclose

P1189

Antioxidant gene polymorphism in Romanian patients with and without diabetic neuropathy and type 2 diabetes mellitus

A. Stoian[1], A. Motataianu[2], D. Minodora[3], S. Voidazan[4], M. Stoian[2], C. Banescu[5]
[1]University of Medicine and Pharmacy Targu Mures, Department of Pathophysiology, Targu Mures, Romania, [2]Targu Mures, Romania, [3]University of Medicine and Pharmacy Targu Mures, Department of Laboratory Medicine, Targu Mures, Romania, [4]University of Medicine and Pharmacy Targu Mures, Department of Epidemiology, Targu Mures, Romania, [5]University of Medicine and Pharmacy Targu Mures, Department of Genetics, Targu Mures, Romania

Background and aims: Type 2 diabetes mellitus is a frequent disease and diabetic neuropathy is one of the most common microvascular complications that affect these patients. There are a lot of evidence suggesting the role of oxidative stress and genetic susceptibility in developement and progression of diabetic complication. We investigated the relation between polymorphism in genes related to oxidative stress such as MnSOD Val16Ala and CAT C-262T and the presence of diabetic neuropathy.

Methods: Samples were collected from 85 patients with type 2 diabetes mellitus (54 patients with diabetic neuropathy confirmed through clinical exam and electrophysiological studies and 31 patients without diabetic neuropathy) and 98 healthy controls and genotyped by using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) methods.

Results: Chi square test revealed no significant difference in genotype frequency for type 2 diabetes mellitus patients and healthy controls with a p=0.62 for MnSOD Val16Ala polymorphism and p=0.26 for catalase C-262T polymorphism. We found that MnSOD Val16Ala genotype frequencies were significantly different between patients with type 2 diabetes mellitus with and without diabetic neuropathy $p<0.05$. Individuals carrying Val/Val genotype had a greater risk for diabetic neuropathy comparing with Ala/Ala genotype (OR:1.422, CI: 1.07 to 2.66, p=0.04). We found no statistical difference in patients with diabetes mellitus for catalase C-262T polymorphism (p=0.95).

Conclusion: This study indicates that MnSOD Val16Ala polymorphism may be associated with diabetic neuropathy and the Val/Val genotype may be a risk factor for the disease. Further studies are needed for conclusive results due to the small number of studied cases.

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P1190

Microvasculitis presenting with painful dysaesthesia: a case report

B. Surboeck[1], K. Lindner[1], J. Hainfellner[2], W. Grisold[1]
[1]Kaiser-Franz-Josef-Spital, Neurology, Vienna, Austria, [2]Medical University of Vienna, Neurology, Vienna, Austria

Background and aims: Peripheral neuropathy can be a manifestation of systemic or nonsystemic vasculitis. Nonsystemic vasculitis neuropathy is restricted to peripheral nerves with no evidence of further systemic involvement. It is rare and the prognosis is good with immunosuppressive treatment.

Case Report: A 43-year-old male presented with symmetric painful paraesthesias in his fingers, lower legs and the foot soles. The pain in the feet was severe and allodynic. Prior to admission an unremarkable MR of the cervical spine and brain and a CSF analysis were made. There was no evidence of a paraneoplastic neuropathy or systemic vasculitis. The clinical examination revealed dysaesthesia and allodynia in his feet. The reflexes were preserved. Electrophysiology showed axonal neuropathy and a varying degree of pathology in individual nerves. Thermal detection thresholds were pathologic. A sural nerve biopsy showed an inflammatory neuropathy affecting walls of small and medium scaled vessels with paravasal lymphocytic infiltration without vessel wall necrosis. The muscle revealed neurogenic atrophy without inflammation.

Results: After diagnosis of a microvasculitic neuropathy the patient received methyprednisolon 80 mg/day for one week and a maintainance dose of 40 mg/day. Symptoms improved.

Conclusion: This patient presented a painful symmetric neuropathy, but showed asymmetric changes in electrophysiology. The preservation of reflexes could suggest small fiber neuropathy. Histopathology confirmed the diagnosis of vasculitis and the symptoms improved with steroid therapy.

The classification of this type of neuropathy is difficult, in absence of serologic markers and vessel wall necrosis, and point to a microvasculitis resembling microscopic polyangiits associated neuropathy.

Disclosure: Nothing to disclose

P1191

Variable clinical aspects of neuralgic amyotrophy

M. Suzuki, M. Takeuchi, Y. Shimizu, K. Kitagawa
Tokyo Women's Medical University, Tokyo, Japan

Background and aims: Neuralgic amyotrophy (NA, also known as Parsonage-Turner syndrome) exists in an inherited and an idiopathic form, characterized by sudden attacks of severe neuropathic pain in the shoulder or arm. The idiopathic version is an acute monophasic brachial plexus disorder of unknown cause, but the condition is generally thought to be an immune system.

Methods: We retrospectively reviewed all medical records of our institution from April 2005 to December 2014. We studied clinical manifestations of NA cases, and reviewed the literature.

Results: We identified 4 males and 3 females, aged from 35 to 71 year-old. Two revealed anti-ganglioside antibodies. Two had herpes zoster virus infection and one had hepatitis E infection precedentially. A residural pain case had also tendonitis in the long head of biceps brachii muscle, which is a cause of frozen shoulder. MRI was useful to see swelling of the nerve trunks and evidence of denervation involving muscles. 6 had intravenous immunoglobulin (IVIG) therapy and 2 of them also had methylprednisolone pulse therapy (MPPT), revealed favourable response, especially for their pain. 2 showed recurrence course. In the literature, some NA cases showed good response for IVIG.

Conclusion: Medical interrogation in detail is most important to diagnose for NA. IVIG or MPPT may be one of potential therapeutics for NA, however the efficacy remains to be established.

Disclosure: Nothing to disclose

P1192

Evaluation and comparison of quality of life scores of polyneuropathy due to Fabry disease and diabetes mellitus

H. Turker[1], K. Akpinar[2], A.O. Bayrak[3], N. Cengiz[4]
[1]Samsun, Turkey, [2]Vezirkopru State Hospital, Neurology, Samsun, Turkey, [3]ondokuz mayıs university, Neurology, Samsun, Turkey, [4]Ondokuzmayis University, Faculty of Medicine, Neurology, Samsun, Turkey

Background and aims: Polyneuropathy due to Diabetes Mellitus is acquired, while Fabry Polyneuropathy is caused by a rare metabolic disorder. Both polyneuropathies have impacts on motor, sensory and autonomic funtions and may effect one or two of them more predominantly. In this study we aimed to investigate and compare the affects of these polyneuropathies on quality of life.

Methods: 18 Fabry patients from the same family aged between 8 and 51 years and 18 Type 2 diabetic patients aged between 50 and 60 were enrolled in the study. Detailed neurological examination, electroneuromyography, Lanss and DN4 tests, life quality scores and Beck Depression tests were performed for each patient.

Results: In Fabry group, 1 of the patients had axonal polyneuropathy, while 15 of the diabetic patients had mixed and 3 of them had axonal polyneuropathy. Patients in both groups had scores over 12 in Lanss and over 4 in DN4 meaning they all had neuropathic pain. Lanss scores were statistically significantly higher in the diabetic group ($p<0.05$). Beck Depression test scores did not show any statistically meaningful differences between the two groups ($p>0.05$). Life quality index scores for diabetic patients were statistically significantly worse than the Fabry group ($p<0.05$).

Conclusion: Fabry disease affects unmyelinated fibers at younger ages when compared to the diabetic patients whose myelinated fibers are influenced predominantly. Both diseases deteriorate quality of life, which seems to begin at younger ages in the Fabry group. Having information about these facts of both diseases can help therapy strategies and taking early precautions.

Disclosure: Nothing to disclose

Ageing and dementia 2

P1201

Inferior parietal cortex hypoperfusion is the most specific to Alzheimer's disease with positive CSF biomarkers

D. Andriuta[1], V. Moullart[2], S. Schraen[3], M.-E. Meyer[2], O. Godefroy[1]
[1]University Hospital of Amiens, Neurology, Amiens, France, [2]University Hospital of Amiens, Nuclear Medicine, Amiens, France, [3]University Hospital of Lille, Biology and Pathology, Lille, France

Background and aims: Regional brain hypoperfusion occupy an essential place in recently formulated diagnostic criteria for Alzheimer's disease (AD). Our objective was to determine the SPECT hypoperfusion pattern in patients with CSF AD signature (1st: abnormal Aß1-42 and abnormal t-tau or p-tau; 2nd: p-tau/Aß1-42 > 0.11) and to evaluate its diagnostic accuracy in a clinical population of the Amiens academic Memory Clinic.

Methods: This retrospective study selected 120 patients, examined in Amiens Memory Clinic, with a lumbar puncture (with a CSF biomarkers (Aß1-42, t-tau and p-tau) measurement), imaged with a cerebral HMPAo SPECT and a cerebral MRI. Clinical diagnoses were: suggestive of AD (n=34), possible or probable AD (n=29), others causes of cognitive impairment (n=57). SPECTs were semiquantitative rated by a nuclear practitioner blinded to clinical and biological data. Beforehand 9 regions of interest were determined.

Results: CSF AD signature (abnormal Aß1-42 and abnormal t-tau or p-tau: n=24; p-tau/Aß1-42: n=45) was associated with inferior parietal ratio minus lateral dorsal frontal ratio (OR: 0.906; 95%CI: 0.835-0.983, p=0.017). This pattern discriminates patients with CSF AD signature (1st) from patients with others causes of cognitive impairment with a sensitivity of 71%, a specificity of 65%, a negative predictive value (NPV) of 90% and a positive predictive value of 33%.

Conclusion: Hypoperfusion in the inferior parietal area was the most sensitive and specific feature of AD diagnosed using clinical and CSF biomarkers criteria. This pattern had a NPV of 90%, and so was highly useful to discriminate AD from others causes of cognitive impairment.

Disclosure: Nothing to disclose

P1202

Neuronal correlates of anosognosia for memory impairment in Alzheimer's disease: the role of posterior cingulate cortex.

N. Antoine, E. Amico, M.A. Bahri, C. Bastin, E. Salmon
University of Liège, Cyclotron Research Centre, Liege, Belgium

Background and aims: Anosognosia for memory deficits has major impact on caring for Alzheimer's disease (AD). However, the neural mechanisms of anosognosia in AD remain unclear. The aim of this study was to acquire multimodal brain imaging in a sample of patients, to evaluate the contribution of brain regions to anosognosia in AD. Here are the functional analysis results with a new and original methodology for the investigation of resting-state functional Magnetic Resonance Imaging (fMRI) spatial pattern.

Methods: Functional connectivity of cerebral areas is not a static phenomenon, but exhibits spontaneous fluctuations over time. Point process analysis applied on functional data has revealed that much of the information regarding brain connectivity is contained in a fraction of critical time points of a resting state dataset. Resting-state fMRI volumes on 31 patients with probable AD were acquired and reduced to a spatiotemporal point process by selecting time points in the PCC at which the signal is higher than a given threshold. Participants' awareness of current memory functioning was assessed with the memory awareness rating scale. The population was split in two (matched) groups following the degree of awareness for memory deficit.

Results: Anosognosic patients demonstrated decreased connectivity between the PCC and the left temporoparietal junction, the ventromedial prefrontal cortex and the superior temporal cortex.

Conclusion: The PCC is a hub region of the default mode network (DMN), notably involved in self-referential processing. These new results suggest that the disturbance of the PCC with others regions of the DMN are implicated in loss of self-knowledge in AD.

Disclosure: Nothing to disclose

P1203

Effectiveness of physical exercise training in elderly with mild to moderate dementia

A. Zamfirescu[1], A. Mirsu-Paun[2], A.A. Capisizu[3], S.M. Aurelian[4], M. Slavila[5], I. Omer[6], A.S. Nica[7], A. Capisizu[4]

[1]"Sf. Luca" Hospital, Clinic of Geriatrics and Gerontology, Bucharest, Romania, [2]University of Medicine and Pharmacy ,,Carol Davila", Bucharest, Romania, [3]University of Medicine and Pharmacy ,, Carol Davila" Bucharest, Pediatric Neurology , Bucharest, Romania, [4]University of Medicine and Pharmacy ,,Carol Davila", Clinic of Geriatric, Bucharest, Romania, [5]"Sf. Luca" Hospital, BRMC, Bucharest, Romania, [6]"Sf. Luca" Hospital, Psychology, Bucharest, Romania, [7]National Institute of Rehabilitation "Filantropia", Rehabilitation, Bucharest, Romania

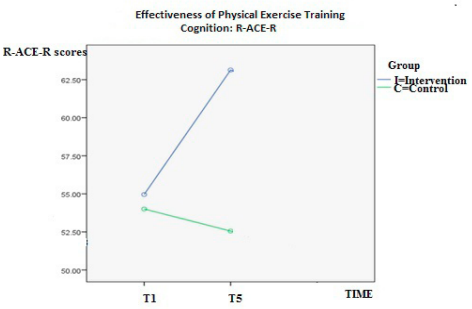
Background and aims: To study the effectiveness of physical exercise training as a treatment opportunity in elderly diagnosed with mild to moderate dementia in addition to pharmaceutical therapy.

Methods: Longitudinal randomized study; 40 participants with mild to moderate dementia (AD, mixed or vascular), no major motor function impairment; randomized in 2 groups: with physical exercise training intervention(I): 5/7, 12 weeks (20 participants) and control group(C) (20 participants). We assessed cognitive and global evaluation scores (MMSE, Clock Drawing Test, R-ACE-R: Addenbrooke's Cognitive Examination/Romanian-version, Reisberg), functional tests (ADL, IADL), neuropsychiatric inventory (NPI-Q), GDS (Geriatric Depression Scale short version), QOL-AD (quality of life in AD) and SPPB(Short Physical Performance Battery). Follow-up after inclusion at 3, 6, 9 and 12 weeks (T1-T2-T3-T4-T5).

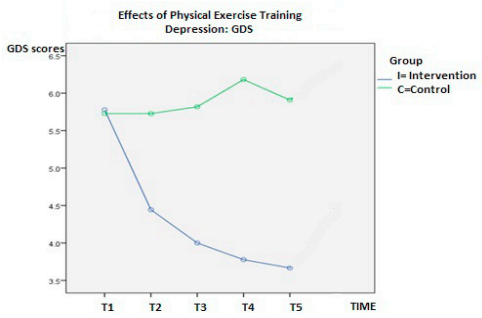
Results: Groups were homogenous at inclusion (T1), mean age:79.35, 80% women, 90% from urban area. 5 patients withdrew from the study. Statistically significant differences between groups at T5 were for: Clock Drawing Test[t(32)=3.28, p<0.005], total R-ACE-R [t(32)=2.28, p<0.005], R-ACE-R subscores: F(verbal-fluency)[t(32) =4.26, p<0.001] and VS(visuo-spatial)[t(32)=3.37, p<0.005], IADL[t(32)=2.06, p<0.005], GDS[t(32)=-2.28, p<0.005], QOL-AD[t(32)=2.06, p<0.005] and SPPB[t(32) =2.30, p<0.05] for 5 chair stands test: t(32) = 2.82, p<0.005.

Test	Group I (intervention with Physical Exercise Training) Group C (control)	Mean scores at T5 (after 12 weeks from inclusion)	Standard Deviation
Clock Drawing Test	I	8.00	1.871
	C	5.65	2.290
R-ACE-R	I	63.37	15.20
	C	52.55	12.26
F (verbal-fluency) (R-ACE-R subscore)	I	8.79	2.234
	C	5.99	1.531
VS (visuo-spatial) (R-ACE-R subscore)	I	12.00	2.806
	C	8.50	3.231
REISBERG	I	2.71	1.213
	C	3.18	1.425
IADL (Instrumental Activities of Daily Living)	I	5.35	1.801
	C	4.12	1.691
QOL-AD	I	34.35	6.103
	C	29.88	6.518

Mean scores of tests at T5 (after 12 weeks from inclusion) with statistically significant differences between I (intervention with Physical Exercise Training) and C (control) groups.



Evolution of R-ACE-R scores from T1 (inclusion) to T5 (12 weeks) for I (intervention with Physical Exercise Training) and C (control) groups.



Evolution of GDS scores from T1 (inclusion) to T5 (12 weeks) for I (intervention with Physical Exercise Training) and C (control) groups.

Conclusion: Physical exercise training proves to be an effective intervention for elderly with mild to moderate dementia, with positive results in cognitive (especially executive function) and functionality scores, with supplementary benefits on mood disorders (reduces depression), improving the quality of life of patients with dementia.

Disclosure: Nothing to disclose

P1204

White matter degeneration in atypical Alzheimer's disease

F. Caso[1], F. Agosta[1], D. Mattavelli[1], R. Migliaccio[2], E. Canu[1], G. Magnani[3], A. Marcone[4], M. Copetti[5], M. Falautano[3], G. Comi[3], A. Falini[6], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]Groupe Hospitalier Pitié-Salpêtrière, Brain and Spine Institute, Paris, France, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neuroscience, Milan, Italy, [5]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [6]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To assess white matter (WM) tract damage in patients with atypical Alzheimer's disease (AD), including early age-of-onset AD (EOAD), logopenic variant of primary progressive aphasia (lvPPA) and posterior cortical atrophy (PCA) using diffusion tensor MRI, and to identify similarities and differences across the AD spectrum.

Methods: WM tract damage and cortical atrophy were assessed in 28 EOAD, 12 lvPPA and 13 PCA patients relative to age- and sex-matched healthy subjects. Conjunction and interaction analyses were used to define overlapping and syndrome-specific patterns of brain damage.

Results: EOAD, lvPPA and PCA patients shared a common pattern of WM damage involving the body of the corpus callosum, fornix, and main anterior-posterior pathways, and cortical atrophy of the left temporo-parietal regions and precuneus. EOAD patients had also a specific damage to the genu and splenium of the corpus callosum, and parahippocampal tract bilaterally. In all AD patients, particularly in the two focal forms (lvPPA and PCA), WM damage was more severe and widely distributed than expected on the basis of cortical atrophy.

Conclusion: In atypical AD clinical phenotypes, the distribution of WM damage exceeds cortical atrophy and may reflect the dissemination of pathology through structural connections from atrophic to unaffected cortical regions. WM degeneration may be an early marker of AD pathology in EOAD and focal AD forms.

Disclosure: Italian Ministry of Health (Grant #GR-2010-2303035).

P1205

Selective FDG-PET changes on right amygdala and temporal pole predict impairments of socio-emotional processing in the behavioural variant of frontotemporal dementia

C. Cerami[1], A. Dodich[2], C. Crespi[2], N. Canessa[3], S. Iannaccone[4], A. Marcone[4], S. Cappa[3], D. Perani[2]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neurosciences, Milan, Italy, [2]Vita-Salute San Raffaele University, Milan, Italy, [3]San Raffaele Scientific Institute, Milan, Italy, [4]San Raffaele Hospital, Milan, Italy

Background and aims: The behavioural variant of frontotemporal dementia (bvFTD) is characterized by socio-emotional processing abnormalities ranging from mild emotional blunting to loss of sympathy and empathy or inappropriate social behaviours. In this study, we evaluate [18F] FDG-PET correlates of social cognition impairments in bvFTD.

Methods: 15 probable bvFTD patients were enrolled. An experimental neuropsychological battery assessed different facets of social cognition (i.e., knowledge of social norms, emotions recognition, affective and cognitive empathy and attribution of intentions and emotions). 19 cognitively normal subjects were included in the behavioural analysis as control group. Each patient underwent a [18F]FDG-PET scan with an optimized method of voxel-based normalization and comparison analyses. Correlations analyses between behavioural performances and the metabolic values were performed on fronto-temporal and limbic Region of Interests (ROIs) according to know brain networks involved in social cognition functioning.

Results: Compared to controls, bvFTD displayed significant lower performances on all social tasks. Right amygdala emerged as key structure for all the investigated abilities of social cognition. Additionally, right temporal pole correlated with affective empathy and ToM, and recognition of emotions from facial expression. Noteworthy, a significant correlation between the disgust recognition and left insula metabolism was also identified.

Conclusion: The presence of right limbic and temporal metabolic changes in bvFTD predicts low performances on socio-emotional tasks, particularly in those involving affective-emotional cues. Insula metabolic changes are responsible of disgust recognition impairment. Selective disease-specific vulnerability on social cognition networks hubs may be detected by voxel-based [18F]FDG-PET analysis, even at the individual level.

Disclosure: This work has been partially supported by the MIUR grant "I meccanismi neurocognitivi alla base delle interazioni sociali" (PRIN2010XPMFW4_008), and by the Università degli Studi di Milano-Bicocca CARIPLO grant „Dottorato ad alta Formazione in Psicologia Sperimentale, Linguistica e Neuroscienze Cognitive". Dr. Cerami was funded by Fondazione Eli-Lilly (Eli-Lilly grant 2011 „Imaging of neuroinflammation and neurodegeneration in prodromal and presymptomatic Alzheimer's disease phases")

P1206

Self-assessment of change in driving in relation to current driving performance on a driving simulator in patients with various neurological conditions

A. Economou[1], M.H. Kosmidis[2], I. Beratis[3], A. Liosidou[3], E. Papadimitriou[4], G. Yannis[4], S. Papageorgiou[3]
[1]University of Athens, Department of Psychology, Athens, Greece, [2]Aristotle University of Thessaloniki, Department of Psychology, Thessaloniki, Greece, [3]"Attikon" University General Hospital, Department of Neurology, Athens, Greece, [4]National Technical University of Athens , Department of Transportation Planning and Engineering, Athens, Greece

Background and aims: To examine self-assessment of driving change in relation to objective driving measures derived from a driving simulation experiment in neurology patients and controls. Perception of change in driving ability with age and cognitive decline is important for the self-monitoring of driving and the realistic adaptation to challenging driving situations. Such situations are difficult to investigate during on-road driving.

Methods: Participants: In these analyses, 157 drivers participated: 65 controls (> 43 years), 50 mild cognitive impairment (MCI) patients, 23 mild Alzheimer's disease (AD) patients, and 19 Parkinson's disease (PD) patients. Different numbers of participants entered different analyses. Measures: Questionnaire measures: Selected questions from a driving behaviour questionnaire asking the driver to rate his driving in a variety of driving environments and conditions in relation to 5 years prior on a 5-point Likert scale. Driving measures: Average speed (in km), average lateral position (distance of the vehicle from the right road border in meters), headway average (average distance from the vehicle ahead in meters), number of times of speed limit violations, number of crashes at unexpected incidents.

Results: Average speed, lateral position, and headway average were z-transformed based on the entire control sample of 102 participants and participants' z-scores were correlated with responses to the self-rating questions. The driving measures were poorly associated with self-rating performance.

Conclusion: Self-rating of driving change is not related to objective performance, though the slower speed and greater headway distance of the AD and PD patients may reflect an adaptation to decline in abilities.

Disclosure: National Strategic Reference Framework (NSRF 2007-13, O.P. "Thales")

P1207

Abstract cancelled

P1208

Grey matter and white matter MRI markers of cognitive progression in early and late onset variants of Alzheimer's disease

F. Agosta[1], F. Caso[1], D. Mattavelli[1], M. Copetti[2], G. Magnani[3], E. Canu[1], A. Marcone[4], M. Falautano[3], G. Comi[3], A. Falini[5], M. Filippi[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neuroscience, Milan, Italy, [5]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To assess grey (GM) and white matter (WM) MRI measures as predictors of cognitive progression in early-onset (EOAD) and late-onset Alzheimer's disease (LOAD).

Methods: T1-weighted and diffusion tensor (DT) MRI was obtained from 48 LOAD and 28 EOAD, who were followed prospectively with 6-month clinical and neuropsychological evaluations (mean follow-up: 12.9 months [maximum: 43.4 months]). At baseline, regional GM and WM damage was evaluated. Longitudinal linear models assessed cognitive changes over time and relationships between MRI and cognitive evolution.

Results: At a similar stage, EOAD presented with more severe multidomain cognitive deficits, greater brain atrophy, but similar WM tract damage relative to LOAD. Compared with LOAD, EOAD patients showed a faster progression during follow-up, mainly in executive, memory and language domains. In EOAD, baseline atrophy of the cingulate, frontotemporal and parietal GM was related to the executive function worsening, while damage to corpus callosum, cingulum, frontotemporal and frontoparietal connections bilaterally predicted the visuospatial abilities deterioration. In LOAD, volumes of the left anterior cingulum, insula, inferior frontal and parietal cortices contributed to executive deficit progression, while the memory decline was predicted by damage to corpus callosum, cingulum and frontotemporal and frontoparietal tracts bilaterally.

Conclusion: In addition to GM atrophy, WM damage contributes to cognitive progression in both LOAD and EOAD, with differences between the two variants probably related to a distinct distribution of pathological abnormalities. DT MRI could be considered an additional biomarker of neurodegeneration predictive of cognitive impairment years later in AD.

Disclosure: Italian Ministry of Health (#GR-2010-2303035).

Cerebrovascular diseases 2

P1209

The neuroprotective effect of cilnidipine in an animal model of ischemic stroke

H. Choi[1], D. L. Koo[2], K.-Y. Lee[1], Y.J. Lee[1], S.-H. Koh[1]
[1]Department of Neurology, Hanyang University College of Medicine , Seoul, Korea, Republic of, [2]Department of Neurology, Seoul National University Boramae Hospital, Seoul, Korea, Republic of

Background and aims: Cerebral infarction causes permanent neuronal loss, which is associated with severe morbidity and mortality. Because hypertension is the main risk factor for cerebral infarction and most patients with hypertension take daily antihypertensive drugs, the neuroprotective effects and mechanisms of those drugs need to be investigated. cilnidipine, a long-acting, second-generation 1,4-dihydropyridine inhibitor of L- and N-type calcium channels has been reported to reduce oxidative stress in our previous study. In this study, we confirmed whether cilnidipine has therapeutic effects in an animal model of cerebral infarction.

Methods: After determination of cilnidipine, a total of 128 rats were subjected to middle cerebral artery occlusion (MCAO). Neurobehavioral function test and brain MRI were performed similar infarct sized rats are randomized to either cilnidipine treatment group or control group. Drug treatment was performed with reperfusion after 2 hrs occlusion. Western blots and immunohistochemistry were also performed after 24 hr occlusion.

Results: Initial infarct volume on DWI was not significantly different in cilnidipine treatment group and control group. But FLAIR MRI at 24 hrs showed significantly reduced infarct volume in cilnidipine treatment group compared with control group. cilnidipine treatment significantly decreased the number of TUNEL-positive cells compared to control group. Western blot and immunohistochemistry showed increased expression of phosphorylated Akt (Ser473) and Bcl-2 and decreased expression of Bax and cleaved caspase-3.

Conclusion: These results suggested that pretreatment with cilnidipine had a neuroprotective effect in ischemic brain and this property is one of the important profiles that are implicated in brain protection.

Disclosure: Nothing to disclose

P1210

Posterior reversible encephalopathy syndrome – clinical and radiological characterization of a six-year Portuguese case series

A. Costa[1], J. Filipe[2], C. Reis[2], E. Azevedo[1], P. Abreu[1]
[1]Centro Hospitalar S. João, Neurology, Porto, Portugal, [2]Centro Hospitalar S. João, Neuroradiology, Porto, Portugal

Background and aims: Posterior reversible encephalopathy syndrome (PRES) is diagnosed by suggestive clinical manifestations and radiological criteria. Our aim was to relate clinical manifestations, aetiology and prognosis with MRI features.

Methods: A retrospective analysis of clinical and radiological data of PRES patients was performed in a central university hospital from 2008-2014. Kruskal-Wallis one-way analysis of variance (statistical significance $p<0.05$) was used to compare categorical data.

Results: 13 patients (9 women) with a median age of 35 years (range: 11-74) were included. Most frequent onset clinical manifestations were seizures (n=9) and visual abnormalities (n=4). Most prevalent PRES aetiologies were acute high blood pressure (n=9) and immunosuppression (n=4). MRI was performed in all patients (time until MRI - median: 4 days, range: 1-12). The following brain MRI patterns were observed, according to lesions distribution: holohemispheric (n=3), isolated superior frontal sulcal (n=3) and parietoccipital (n=5). Partial expression of the above patterns was observed in 2 patients. Concomitant focal areas of diffusion restriction were evident in 7 patients. Focal haemorrhages were found in 3 patients and sulcal subarachnoid haemorrhage in 2 patients. Cortical and/or leptomeningeal areas of contrast enhancement (n=3) were related to seizures (p=0.026), consciousness impairment at onset (p=0.048) and death (p=0.026). We found no association between other clinical features and MRI.

Conclusion: Nowadays MRI is mainly used to accurately diagnose PRES in a patient with suggestive clinical manifestations. Defining MRI patterns, presence of ischemic, haemorrhagic lesions and contrast enhancement may be additional important information to monitor the disease and to determine its prognosis.

Disclosure: Nothing to disclose

P1211

Impact of serum thyroid-stimulating hormone on functional outcome in patients with acute ischemic cerebrovascular event

B. Delpont, C. Aboa-Eboulé, J. Durier, B. Daubail, M. Giroud, Y. Béjot
Dijon Stroke Registry, EA4184, University Hospital and Medical School of Dijon, Neurology, Dijon, France

Background and aims: Hypothyroidism may influence outcome of patients with ischemic stroke. We evaluated the association between serum thyroid-stimulating hormone (TSH) levels at admission and functional outcome at discharge in patients with acute ischemic cerebrovascular event.

Methods: Patients with acute ischemic stroke or TIA who were admitted to the department of Neurology of the University Hospital of Dijon, France, were identified between January 2010 and December 2011. Demographic and clinical data including initial clinical severity were recorded. Serum TSH was measured within the first 18h of onset. TSH levels were analysed according to the tertiles of their distribution (<0.902 vs 0.902-1.67 vs >1.67 mmol/L). Associations between TSH levels and functional outcome at discharge assessed by the modified Rankin scale score were analyzed using ordinal logistic regression models.

Results: 934 patients (mean age 71.8 ± 22.2, 61% men) were recorded including 731 ischemic strokes and 203 TIAs. In multivariable analyses, high TSH levels at admission were associated with a better functional outcome at discharge (OR=0.39; 95% CI: 0.28-0.55, p<0.001 for tertile 2 vs tertile 1; OR=0.39; 95% CI: 0.29-0.56, p<0.001 for tertile 3 vs tertile 1). Consistent results were observed when considering stroke patients only (OR=0.43; 95% CI: 0.31-0.60, p<0.001 for tertile 2 vs tertile 1; OR=0.44; 95% CI: 0.31-0.62, p<0.001 for tertile 3 vs tertile 1).

Conclusion: High TSH levels are associated with better functional outcome in patients with acute ischemic cerebrovascular event, independently of confounding variables including initial severity. Neuroprotective properties or neuroplatic changes could be involved to explain this finding.

Disclosure: Nothing to disclose

P1212

Recurrent episodes of acute reversible encephalopathy: the first Greek case of 'CADASIL-coma'

G. Dervenoulas[1], M. Ragno[2], L. Pianese[3], G. Velonakis[4], M. Papathanasiou[5], C. Arvaniti[1], S. Papageorgiou[1], G. Tsivgoulis[1], A. Bonakis[1], P. Toulas[4], L. Stefanis[1]
[1]University of Athens, Attikon University Hospital, Second Department of Neurology, Athens, Greece, [2]Mazzoni Hospital, Division of Neurology, Ascoli Piceno, Italy, [3]Mazzoni Hospital, Molecular Medicine Section, Ascoli Piceno, Italy, [4]University of Athens, Research Unit of Radiology and Medical Imaging, Athens, Greece, [5]University of Athens, Attikon University Hospital, Second Department of Radiology, Athens, Greece

Background and aims: The cardinal clinical features of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infracts and Leucoencephalopathy (CADASIL), are recurrent strokes, migraine, cognitive impairment and psychiatric disturbances. The disease is caused by mutations in the notch3 gene on chromosome 19. The clinical course is variable and atypical phenotypes such as acute reversible encephalopathy have been reported.

Case Report: We describe a CADASIL case with a rare phenotype.

Results: A 64-year-old female patient of Caucasian origin, was referred to our Department with an acute encephalopathy preceded by an episode of severe migraine. Her past medical history included migraine since she was in her 20s, arterial hypertension, hyperuricemia. Significantly, over the past nine years she had had three similar episodes of reversible encephalopathy without a definite diagnosis. During the first episode she had developed generalized tonic-clonic seizures and was since then under treatment with valproic acid. She was also under treatment with fluoxetine due to a mood disorder with mild depressive symptoms. On admission, she was disorientated and confused with limited speech content and she gradually entered an apathetic state. Clinical examination revealed mild right hemiparesis and mild pyrexia (<37.4°C). CSF examination was normal and EEG showed slow wave activity across the left hemisphere. MRI findings were classic for CADASIL. Ten days later she made full recovery. Genetic testing is under way to molecularly confirm the diagnosis of reversible encephalopathy in the context of CADASIL.

Conclusion: CADASIL should be considered as possible diagnosis in patients presenting with reversible encephalopathy, especially when combined with migraine and stroke-like episodes.

Disclosure: Nothing to disclose

P1213

Carotid artery intima-media thickness as a marker of small or large vessel disease in ischemic stroke

F.J. Díaz de Terán[1], P. Martínez Sánchez[1], B. Fuentes Gimeno[1], J. Rodríguez Pardo De Donlenbún[1], C. Calle De Miguel[1], J. Pérez Lucas[1], E.M. Alba Suarez[1], I. Illán Gala[1], J. Máñez Miró[1], B.E. Sanz Cuesta[2], G. Ruiz Ares[3], E. Díez Tejedor[1]
[1]Hospital Universitario La Paz, Neurology, Madrid, Spain, [2]Madrid, Spain, [3]Hospital La Paz, Neurology, Madrid, Spain

Background and aims: Some studies relate the carotid intima media thickness (IMT) to small vessel disease (SVD) whilst others relate it to atheromatous large vessel disease (LVD). Our objective was to study the impact that has IMT in each of these entities, analysing their relationship in patients with cerebral infarction (CI).

Methods: Observational cohort study including CI patients. Study period: 2010-2014. Duplex carotid ultrasonography was performed in all patients during the first 48 hours after admission and mean IMT as well as the presence of atheroma plaques were recorded. SVD was defined as the presence of lacunar infarcts or moderate-important leukoaraiosis in neuroimaging, and LVD as extra/ intracranial brain arteries atheromatosis. Patients were classified into 4 groups: 1) SVD, 2) LVD, 3) SVD+LVD and 4) not SVD nor LVD. Multiple linear regression analyses were conducted to evaluate the association between SVD/LVD and IMT

Results: Overall, 823 patients were included, 57.2% male, mean age 70.9 years. Multivariate analysis showed that SVD (beta coefficient [ET]=0.050 [0.0197]) as well as LVD (Beta coefficient [SE]=0.048 [0.0167]) were related to mean IMT, being this association higher in case of SVD+LVD group (beta coefficient [SE]= 0.065 [0.0171]). Bonferroni test showed that the greatest difference was between the SVD+LVD and the group without SVD or LVD.

Conclusion: Both SVD and LVD are associated with mean IMT and this association is greater when they coexist. This non-invasive and easily reproducible measure is a useful tool to estimate vascular damage what could contribute to a more effective prevention.

Disclosure: Nothing to disclose

P1214

Transplantation of adult subventricular zone derived neural progenitor cells – an analysis of optimal cell delivery routes and their underlying mechanisms of action

T. Doeppner[1], B. Kaltwasser[1], M. Teli[2], E. Sanchez-Mendoza[1], E. Kilic[3], M. Bähr[4], D.M. Hermann[5]
[1]University Hospital Essen, Neurology, Essen, Germany, [2]National Institute of Technology Calicut, Kerala, India, [3]Istanbul, Turkey, [4]University Hospital of Goettingen, Goettingen, Germany, [5]Essen, Germany

Background and aims: With neuroprotective approaches having failed until recently, focus on experimental stroke research has switched towards manipulation of post-ischemic neuroregeneration. Transplantation of neural progenitor cells (NPCs) is a promising strategy for promotion of neurological recovery. Yet, fundamental questions including the optimal cell delivery route still have to be addressed.

Methods: C57BL6 mice were exposed to transient focal cerebral ischemia and allowed to survive for as long as 84 days post-stroke. At six hours post-stroke, NPCs were grafted using six different cell delivery routes, i.e. intravenous, intraarterial, ipsilateral intrastriatal, contralateral intrastriatal, ipsilateral intraventricular and intracortical injection. Control mice received PBS only.

Results: Intralesional numbers of GFP+ NPCs were high after ipsilateral intrastriatal transplantation, whereas other injection paradigms yielded small numbers of grafted cells. However, acute neuroprotection and improved functional outcome was observed after both systemic (intraarterial and intravenous) and ipsilateral intrastriatal transplantation. Whereas systemic cell delivery induced acute and long-term neuroprotection, reduction of brain injury after ipsilateral intrastriatal cell grafting was only temporary, in line with the loss of transplanted NPCs in the brain. Both systemic and ipsilateral intrastriatal NPC delivery reduced microglial activation and leukocyte invasion, reducing free radical formation within the ischemic brain. Noteworthy, only systemic NPC administration stabilized the blood-brain-barrier and reduced leukocytosis in the blood. Although intraarterial NPC transplantation was as effective as intravenous cell grafting, mortality of stroke mice was high using this delivery route.

Conclusion: Intravenous delivery of NPCs in our experimental model is an attractive and effective strategy for stroke therapy that deserves further proof-of-concept studies.

Disclosure: Nothing to disclose

P1215

The bed cycling test: a bedside test for unilateral cerebral dysfunction

K. Feil[1], N. Boettcher[1], F. Lezius[2], T. Hoegen[3], K. Huettemann[3], C. Muth[1], E. Ozan[1], F. Schoeberl[1], A. Zwergal[1], O. Bayer[4], M. Strupp[1]
[1]*University Hospital, Department of Neurology and German Center for Vertigo and Balance Disorders, Munich, Germany,* [2]*University Clinic Charité, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany,* [3]*University Hospital, Department of Neurology, Munich, Germany,* [4]*University Hospital, German Center for Vertigo and Balance Disorders, Munich, Germany*

Background and aims: Analogously to the forearm rolling test to detect unilateral upper limb dysfunction a so-called bed cycling test (BCT) was developed and evaluated to detect mild to moderate unilateral lower limb dysfunction and compared to the leg holding test.

Methods: In a prospective examiner-blinded study 60 patients with MRI or CT proven acute focal cerebral hemisphere lesions and a mild to moderate unilateral paresis of the lower limb (graduated 3-4/5 on MRC scale) and 60 control persons with normal imaging and without obvious focal signs were examined using a battery of clinical tests including the filmed BCT and leg holding test. Nine examiners, who were blinded to the diagnosis, evaluated these tests presented to them on videos.

The Example patient performing bed cycling test (BCT). Patient is lying on his back. Both legs are flexed in the hip. The patient is asked to air cycle rapidly with closed eyed forwards for 10 seconds and backwards for 10 seconds (bed cycling test).

Results: The BCT was rated right positive in 35.5% compared to leg holding test in 26.0%. Examiners had false negative results in 29.1 % of cases using BCT and 44.7% using leg holding test. In 36.7% only BCT was pathological while leg holding test was unremarkable, In conclusion BCT is more sensitive (64.3%) than leg holding test (46.2%) while the specificity of leg holding test (85.6%) is higher than of BCT (70.1%) to detect a cerebral lesion affecting the lower limb.

Conclusion: The BCT is a useful additional clinical bedside test to detect subtle unilateral cerebral lesions, especially when regular neurological examination is unremarkable. The BCT is easy to perform and can be added to the neurological routine examination.

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P1216

Misdiagnosis of the central variant of posterior reversible encephalopathy

A. Félix[1], M. Milheiro[1], N. Fernandes[2], A. Florêncio[2], H. Nzwalo[1]
[1]*Centro Hospitalar do Algarve, Neurology, Faro, Portugal,* [2]*Centro Hospitalar do Algarve, Internal Medicine, Faro, Portugal*

Background and aims: Posterior reversible encephalopathy syndrome (PRES) is a neurological complication characterized by different manifestations associated vasogenic edema in the parietal-occipital lobes. Its central variant (CV) refers to the exclusive or predominant brainstem involvement.

Case Report: A 49-year-old hypertensive woman was admitted to our stroke unit after onset of left homonymous hemianopia. She was stable (170/97 mmHg). Brain MRI showed a right-sided posterior cerebral artery (PCA) ischemic stroke. Recent history was remarkable for diffuse brainstem glioma (DBSG) diagnosed in the previous year, treated with radiotherapy and temozolamide, with complete clinical and radiological remission. DBSG was diagnosed after the finding of "de novo" extensive brainstem lesion on MRI preformed because of hypertensive encephalopathy (HE) manifested with severe headache, confusion and refractory high blood pressure (≥230/130mmHg). The MRI lesion was not present 5 months earlier. Apart from papilledema, the examination was normal. With blood pressure normalization, manifestations disappeared (3 days).

Results: Stroke investigation was negative. The presence of associated radiation induced leukoencephalopathy supported a presumptive diagnosis of radiation-induced PCA disease.

Conclusion: The absence of brainstem signs in a patient with a presumable rapidly growing brainstem lesion and complete resolution during follow up, are unexpected findings of DBSG. On contrary, the triad of HE, remarkable clinical-radiological dissociation and striking total reversibility of any extensive brainstem lesion is highly suggestive of CV of PRES. Because brainstem biopsy is not universally performed in presumed cases of DBSG, considering the diagnosis of this rare variant of PRES is fundamental to avoid unnecessary investigations and treatments.

Disclosure: Nothing to disclose

P1217

No evidence for retinal damage evolving from reduced retinal blood flow in internal carotid artery stenosis

H. Heßler[1], H. Zimmermann[1], T. Oberwahrenbrock[1], E.M. Kadas[1], A. Brandt[1], A. Kauert[2], S.J. Schreiber[3], F. Paul[1]

[1]NeuroCure Clinical Research Center, Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Evangelisches Krankenhaus Königin Elisabeth Herzberge, Neurology, Berlin, Germany, [3]Charité Universitätsmedizin Berlin, Neurology, Berlin, Germany

Background and aims: High-grade internal carotid artery stenosis (CS) may lead to impaired retinal blood flow. The objective of this study was to examine the influence of chronic reduced retinal blood flow in CS on morphological or functional measures of the retina.

Methods: Patients with unilateral CS (lumen reduction ≥50%, ECST-criteria) were grouped according to the grade of the stenosis and the direction of blood flow in the ophthalmic artery (OA). Transorbital duplex ultrasound was performed to assess optic nerve sheath diameter and optic nerve diameter. In addition, retinal perfusion was evaluated by analysis of central retinal artery (CRA) blood flow velocities. Retinal spectral domain optical coherence tomography (OCT) examinations were performed to acquire retinal nerve fibre layer thickness, total macular volume, ganglion cell/inner plexiform layer volume, and optic nerve head volume. Visual function was measured by high- and low contrast visual acuity. Intra-patient inter-eye statistics were performed for all parameters.

Results: 27 CS patients were enrolled (table 1). Eyes with CS ≥80% and retrograde OA blood flow showed a significant reduction of CRA peak systolic velocities (No-CS side: 0.130±0.035 m/s, CS side: 0.098±0.028; p=0.005; n=12; figure 1). OCT, ultrasound and visual functional parameters did not show a significant difference.

		Groups		
		CS 50-79%	CS ≥80% no-retrograde OA	CS ≥80% retrograde OA
Patients N		8	7	12
Sex	male	7 (87,5%)	2 (28,6%)	8 (66,7%)
	female	1 (12,5%)	5 (71,4%)	4 (33,3%)
Age [years]	mean ±SD (min-max)	66 ±4 (61-72)	62 ±7 (50-71)	58 ±12 (35-76)
Grade of CS	50 - 79%	8 (100%)	0	0
	80 - 99%	0	5 (71,4%)	4 (33,3%)
	ICA-Occlusion	0	2 (28,6%)	8 (66,7%)

Table 1: Demografic details for different CS groups. N total = 27. CS = carotid artery stenosis, ICA = internal carotid artery, OA = ophthalmic artery, SD = standard deviation.

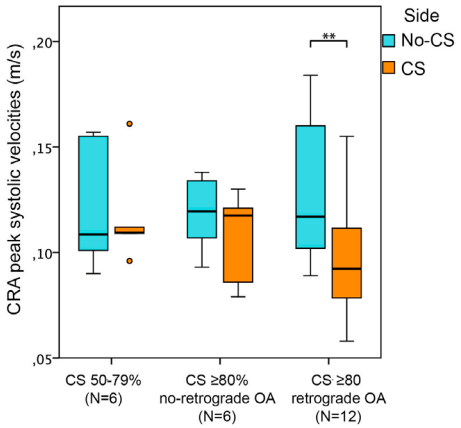

Figure 1: Inter-eye comparison of peak systolic blood flow velocities in the central retinal artery (CRA) for different CS groups. **p<0.01. CS = carotid artery stenosis, OA = ophthalmic artery.

Conclusion: Our data shows that a CS induced hemodynamic impairment of CRA blood flow does not lead to gaugeable morphological or functional changes of the retina. The collateral pathway of the retrograde OA, however, seems to be an important factor for the retinal blood supply.

Disclosure: Nothing to disclose

Cognitive neurology/ neuropsychology 1

P1218

Self-awareness of performance in cognitive testing: differences between healthy elderly and patients with Parkinson's disease (PD)

S. Fragkiadaki[1], N. Andronas[1], I. Beratis[1], D. Kontaxopoulou[1], D. Pavlou[2], A. Liozidou[1], A. Economou[3], G. Yannis[2], S. Papageorgiou[1]
[1]Athens University Medical School, [2]nd Neurology Clinic, Attikon Hospital, Athens, Greece, [2]National Technical University of Athens, School of Civil Engineering, Department of Transportation Planning and Engineering, Athens, Greece, [3]National University of Athens, Department of Psychology, Athens, Greece

Background and aims: The concept of "self-estimation" reflects the ability of an individual to evaluate his own performance with relatively objective terms. A limited number of studies have systematically studied this topic in Parkinson's Disease (PD) patients. The scope of the present study was to compare objective measures of neuropsychological performance with the subjective evaluation of the corresponding performance as well as to investigate differences in the self-assessment profile of PD patients and cognitively intact individuals.

Methods: 28 participants diagnosed with PD (25 males, age=63.13±11.32 years, disease duration=5.26±4.11 years, Hoehn&Yahr=1.9±0.4) and 33 matched for age and education control subjects (30 males, age=59.82±10.27 years) were examined with an extended battery of neuropsychological tests. After every test they were asked to self-evaluate their performance by comparing it to what they considered as average for people of their age and educational level. This self-evaluation was reported on a scale ranging from -100 to +100.

Results: Significant differences were found in the self-assessment patterns of the two groups in episodic memory measures for verbal and visuospatial material as well as on tasks engaging executive, attentional and reaction time resources. PD patients overestimated their performance on attentional and visuospatial tasks while control participants underestimated their performance on measures of verbal and visuospatial episodic memory.

Conclusion: The current results indicate the presence of a generalized difficulty of patients with PD in assessing their performance on neuropsychological measures that could reflect an impairment in monitoring mechanisms due to their neurological condition.

Disclosure: Nothing to disclose

P1219

Amnestic mild cognitive impairment due to Alzheimer's disease is specifically characterized by APOE4 status but not mesial temporal atrophy using a visual rating scale

D.A. García-Estévez[1], M. Marey-Garrido[2], J.A. Bravo-Ricoy[3]
[1]Hospital Comarcal de Monforte de Lemos, Unit of Neurology, Monforte de Lemos, Spain, [2]Hospital Comarcal de Monforte de Lemos, Radiology Sevice, Monforte de Lemos, Spain, [3]Hospital Comarcal de Monforte de Lemos, Epidemiology Service, Monforte de Lemos, Spain

Background: The use of biomarkers (total-Tau, phospho-Tau, amyloid-β peptide) in the cerebrospinal fluid (CSF) are useful to identify patients with amnestic mild cognitive impairment (MCI) due to Alzheimer's disease (MCI-AD), and so we could start the treatment with both drugs and cognitive therapy in this early predementia phase. Other variables as age, severity of temporal atrophy, APOE status, first degree relatives of dementia (FDR) and the score in different cognitive tests could be altered in these patients.

Aim: To identify in a sample of amnestic MCI (aMCI), using the biomarkers of AD in CSF, who have a prodromal AD and which clinical and paraclinical variables characterize them.

Patients and Methods: We have studied 38 patients with aMCI using the Memory Alteration Test (M@T). All of the patients underwent a lumbar puncture and the biomarkers of AD in their CSF were analyzed and the dementia Hulstaert index was calculated. A magnetic resonance imaging was done to measure the atrophy of the hyppocampal and mesial temporal areas using a visual rating scale (MTA rating). The APOE status was determined in all patients.

Results: 28 out of 38 patients were classified as MCI-AD using the Hulstaert index and phospho-Tau value. Comparing with MCI- no AD patients we did not find significative differences in age, M@T score, MTA rating and FA. However, MCI-AD patients were characterized by to be carrier of APOE4.

Conclusion: Patients with aMCI can be diagnosed as prodromal Alzheimer's disease using biomarkers in CSF (Hulstaert index) and APOE status but not by MTA rating.

Disclosure: Nothing to disclose

P1220

Multi-channel EEG analysis of a stimulus dependent deliberation process leading to a decision for releasing an adequate motor command

S. Henz[1], J. Werner[1], D. Kutz[1], W. Hürster[2], F. Kolb[1], J. Nida-Rümelin[3]
[1]University of Munich, Institute of Physiology, Munich, Germany, [2]Research and Consulting, Munich, Germany, [3]University of Munich, Department of Philosophy IV, Munich, Germany

Background and aims: The aim of this study was to determine whether a deliberative process is detectable in EEG recordings. Deliberation was related to an evaluation of short-lasting visual stimuli leading to a decision for releasing adequate motor commands.

Methods: 25 young and healthy, right handed participants had to press one of two buttons in a simple motor task and a color-word Stroop task. In the simple motor task participants knew which button to press, whilst in the color-word Stroop task they had to press with the right index finger when meaning and color coincided, or with the left index finger when meaning and color were disparate.

Results: In simple motor task EEGs a sequence of positive (P) and negative (N) cortical potentials (P1-N1-P2), assumed to be related to the processing of the performed movement, was observed. The sequence was similar in EEGs of participants having to deliberate over how to respond but was preceded by a slowly increasing negativity terminating in a maximum negativity (N0).

Conclusion: The N0 was assumed to represent the end of the deliberation process during the Stroop task. The duration of the increasing slope terminating in N0 may reflect the duration of the deliberation process. Our data suggest the existence of neurophysiological correlates of deliberative processes.

Disclosure: Nothing to disclose

P1221

Seasonal changes in the incidence of transient global amnesia

O. Keret, N. Lev, I. Steiner
Rabin Medical Center, Beilinson Hospital, Department of Neurology, Petach Tikva, Israel

Background and aims: Transient global amnesia (TGA) is a stereotypic condition, characterized by anterograde and retrograde amnesia that typically resolves within 24 hours. The pathophysiology of TGA is still unclear. We noted that patients hospitalized with TGA tend to appear in seasonal clusters. We therefore retrospectively reviewed the monthly occurrence of TGA in our patient population.

Methods: In our department every patient with acute presentation of amnesia is hospitalized for observation and evaluation. We reviewed the prevalence of TGA in our patient population between the years 2005 and 2013.

Results: During this period, 86 patients who met the criteria for TGA were hospitalized. Annual incidence ranged from 4 to 16. There were 32 men and 54 women, their age ranging n 32 to 79, (mean age of 61+10.3). Two prevalence peaks within each year were observed: November-December and March with monthly rate “climbs” and “descends” from each of these peaks.

Conclusion: We are unaware that the seasonal occurrence of TGA was examined before. The hypothesis that TGA is due, at least in some patients, to infection, probably viral, is based on this observation of seasonal distribution of. It should be examined and verified in other cohorts.

Disclosure: Nothing to disclose

P1222

Screening for postoperative delirium in patients with acute hip fracture: assessment of predictive factors

A. Koskdereliogluˡ, O. Onderˡ, M. Gucuyenerˡ, T. Altay², C. Kayali², M. Gedizlioglu¹

¹*Izmir Bozyaka Education and Research Hospital, Department of Neurology, Izmir, Turkey,* ²*Izmir Bozyaka Education and Research Hospital, Departement of Orthopaedics and Traumatology, Izmir, Turkey*

Background and aims: The aim of this study is to estimate the incidence and risk factors of delirium during the early postoperative period following hip fracture surgery. Furthermore, we investigated the accuracy of Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for detection and assessment of delirium.

Methods: We consecutively recruited the patients older than 65 years undergoing hip fracture surgery in the orthopaedics clinic during the study period. The presence of delirium was determined daily by two of the authors according to CAM-ICU criteria. A further evaluation was made with the reference standard DSM-IV criteria for delirium by another author unaware of the former. Their cognitive function was evaluated with the Mini-Mental State Examination (MMSE) and a possible depressive mood with the Beck Depression Inventory (BDI). Baseline characteristics, as well as ASA classification and clinical outcomes were analyzed for the correlation with accompanying delirium.

Results: Among 109 patients, 20 (18.3%) were diagnosed with delirium. The concurrent validity of CAM-ICU was good (kappa=0.84). Specificity was 98.9%, and sensitivity was 80%. Multivariate regression analysis showed that MMSE (p=0.001) and BDI scores (p=0.002) correlated with the occurrence of delirium.

Conclusion: Our results point that CAM-ICU is highly sensitive and specific to identify delirium in hip fracture patients in the postoperative period. Among all of the risk factors, cognitive impairment and depressive mood were strongly associated with postoperative delirium. We suggest that a preoperative assessment of cognition and depression may be useful for identifying patients with higher risk of postoperative delirium.

Disclosure: Nothing to disclose

P1223

Quality of life and neuropsychiatric symptoms in patients with clinically isolated syndrome

J. Laczóˡ, E. Hynčicová², M. Vyhnálek², J. Vecánová², J. Libertínová², I. Kovárová³, T. Nikolai², J. Hortˡ, E. Meluzinová²

¹*International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic,* ²*2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Department of Neurology, Prague, Czech Republic,* ³*1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Department of Neurology, Prague, Czech Republic*

Background and aims: Health-related quality of life is poorer and neuropsychiatric symptoms including depression, anxiety and apathy together with fatigue are more common in patients with multiple sclerosis (MS). These conditions have not been investigated in patients with clinically isolated syndrome (CIS), who are at higher risk of developing MS.

The aim was to describe factors that may influence health-related quality of life and describe which neuropsychiatric symptoms are present in patients with CIS.

Methods: Patients with CIS on interferon-beta (n=44; 8.1±9.5 months on medication; EDSS 1.6±0.7) underwent clinical examination, brain MRI, cerebrospinal fluid assessment and neuropsychological examination including questionnaire measuring health-related quality of life—RAND-36 item Health Survey (SF-36), and following neuropsychiatric scales: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Apathy Evaluation Scale (AES) and Fatigue Severity Scale (FSS). Results were compared to age, gender and education matched healthy controls (n=32).

Results: Patients with CIS had according to SF-36 poorer general health conditions (p<.001), physical functioning (p=.003) and more bodily pain, which interfered with their normal work (p=.001), but were not limited in their life due to physical health. Patients did not manifest increased fatigue on FSS scale. Patients manifested more anxiety (BAI) and depressive (BDI) symptoms but no apathy (AES).

Conclusion: Poorer physical functioning as well as depression and anxiety are reported already in patients with CIS. With exception of bodily pain, they do not interfere with patients' work and activities of daily living. Contrary to previous studies with MS patients, patients with CIS do not report increased fatigue or apathy.

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P1224

Modulation of fMRI amygdaloid activation combined with the recording of electrodermal resistance in response to variations in emotional intensity

B. Louise[1], A. Comte[2], L. Tatu[1], J.L. Millot[3], T. Moulin[1], E. Medeiros de Bustos[1]

[1]CHRU J. Minjoz , Neurology, Besancon, France, [2]INSERM, Fonctional neuroimaging , Besancon, France, [3]Besançon Laboratory of Intergrative and Clinical Neuroscience, Besancon, France

Background and aims: Although the development of functional imaging techniques has established the implication of the amygdala in the emotional process, its specific role remains controversial. The aim of this study was to highlight the sensitivity of the amygdala to emotional intensity (arousal).

Methods: We conducted an analysis of the modulation of amygdala activation according to variation in emotional intensity via an fMRI event-related protocol. Monitoring of electrodermal activity, a marker of psychophysiological emotional perception and which reflects the activation of the autonomic nervous system, was carried out concurrently. 18 subjects (10 men; aged from 22 to 29 years) looked at emotionally positive photographs.

Results: We demonstrated that the left and right amygdalae were sensitive to changes in emotional intensity, activating more in response to stimuli with higher arousal. Furthermore, electrodermal responses were more frequent for the most intense stimuli, demonstrating the concomitant activation of the autonomic nervous system.

Conclusion: These results highlight the sensitivity of the amygdala to the intensity of positive emotions, and in conjunction with results in the literature on negative emotions, prove the role of the amygdala in the perception of intensity.

Disclosure: Nothing to disclose

P1225

Novel computerized neglect test reveals an ipsilesional spatial attention bias in acute right hemisphere stroke patients without hemispatial neglect

B. Machner[1], I. Koenemund[1], P. Bays[2], J. von der Gablentz[1], C. Helmchen[1], A. Sprenger[1]

[1]University of Luebeck, Dept. of Neurology, Lübeck, Germany, [2]University College London, Institute of Neurology, London, United Kingdom

Background and aims: Diagnosis of hemispatial neglect is mainly based on clinical observation and neuropsychological paper-pencil test batteries. We questioned whether right hemisphere stroke patients without clinical signs of neglect and normal performance in established paper-pencil tests may still have an ipsilesional spatial attention bias.

Methods: We investigated 33 acute right hemisphere stroke patients, 20 were assigned to the "Neglect group" based on their pathological performance in a paper-pencil test battery for neglect, 13 with normal test performance constituted the "RBD group" (right brain damage without neglect). Patients, as well as 11 healthy control subjects, underwent a novel computerized visual search task resembling a real life situation, where a paperclip had to be found on a desk among other distractors ("Desk scene", 100 trials). We recorded eye movements and reaction times and analysed the number of trials with correct target detection.

Results: Despite completely normal paper-pencil test performance, RBD patients showed a clear ipsilesional spatial attention bias in the Desk scene. They performed on a better absolute level as compared to the Neglect group, but revealed a similarly steep attentional gradient from right to left. The further left the target, the lower the detection rate and the higher the reaction time. RBD patients' fixations also revealed a mild rightward shift.

Conclusion: There is an ipsilesional spatial attention bias in right hemisphere stroke patients that is not detected by standard paper-pencil tests for neglect. This pathological bias may impair patients in the demanding situations of daily living, which should be considered in the rehabilitation process.

Disclosure: Nothing to disclose

Headache and pain 2

P1226

S-adenosyl methionine (SAMe) reverses the development of tolerance to analgesic activity of morphine in rats

J. Katyal, H. Kumar, D. Joshi, Y.K. Gupta
AIIMS, New Delhi, Pharmacology, New Delhi, India

Background: Chronic administration of morphine results in development of tolerance to its analgesic effects, limiting its clinical usefulness in pain management. Role of S-adenosyl methionine (SAMe) in morphine tolerance was evaluated.

Methods: Morphine tolerance was developed by daily administration of morphine at 3 or 7mg/kg, intraperitoneally (ip) for 5 days. Male Wistar rats (150-250g), were divided into 6 groups (n=6) and received SAMe 800 mg/kg orally (po), morphine 3mg/kg or 7mg/kg (ip), or combination of SAMe followed by morphine either dose 45 min later for 5 days. The analgesic activity was determined using tail flick analgesiometer (Techno, India). In a separate set of experiments, SAMe was administered for five days. On the 4th and 5th day naloxone (1mg/kg), subcutaneous (sc) was given 15 min before SAMe to study opioidergic involvement.

Results: Morphine per se at 3 and 7mg/kg showed tolerance to analgesic activity after day 3 and day 1 respectively. SAMe per se showed analgesic effect after three days of repeated administration. Co-administration of morphine and SAMe reversed morphine tolerance. On the other hand, naloxone per se and when given with SAMe had no significant effect on tail flick latencies.

Conclusion: S-adenosyl methionine not only per se has an analgesic activity but also can reverse the tolerance to analgesic effect of morphine. This analgesic action of SAMe appears to be independent of opioidergic involvement.

Disclosure: Nothing to disclose

P1227

Pain gluten syndromes

S. Kopishinskaya
Nizhniy Novgorod, Russian Federation

Background and aims: Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten. CD, migraine and fibromyalgia (FM) are the common disorders of the population. The aim of the study was to access the prevalence of migraine and FM among CD patients.

Methods: We examined 200 CD patients and 100 patients with reflux esophagitis and without CD from the control group for migraine. All patients fulfilled the headache diary during three months before diagnosis of migraine was made and six months of the gluten diet. They had neurological and instrumental examination and questioned on FM, restless legs syndrome, large and small fibers neuropathies, depression, anxiety.

Results: CD group had the migraine syndrome four times more often than. In CD group the migraine attacks were 2.5 times more frequent, but the duration of the attacks was less long. The migraine attacks in CD group were less intensive and had a late debut. The attacks were more frequent in CD patients who were older than 50 years old. The attacks disappeared in 25% of the CD patients with migraine syndrome who were on the agluten diet and 38% had reduction of the intensity and/or the attacks frequency. FM was three times more frequent in CD patient group (22%).

Conclusion: We revealed the association between the migraine syndrome and CD and the high efficiency of the agluten diet. Also we found the direct correlation between FM and small fibre neuropathy, restless legs syndrome, depression, anxiety in CD patient group.

Disclosure: Nothing to disclose

P1228

Anodal transcranial direct stimulation (tDCS) targeting the anterior cingulate gyrus for the treatment of chronic cluster headache: a proof-of-concept trial

D. Magis, A. Cosseddu, S.L. Sava, K. D'Ostilio, J. Schoenen
headache research unite, neurology, Liege, Belgium

Background: There is a need for better treatments in chronic cluster headache (CCH). In responders to percutaneous occipital nerve stimulation the subgenual anterior cingulate gyrus was found hypermetabolic (Magis et al.2011). We reasoned that activation of this area by transcranial neurostimulation could be effective in CCH.

Aim: To explore the preventive effect of anodal (i.e. activating) transcranial direct current stimulation (tDCS) targeting the anterior cingulate gyrus in CCH patients.

Methods: CCH patients applied tDCS (2mA) daily for 20 minutes during 4 weeks with anode positioned over the forehead (FpZ), and cathode over C7. Therapeutic effects were monitored with paper diaries.

Results: 9 CCH patients were enrolled up to now: 7 completed the trial, 2 were not satisfied and dropped out. In evaluable patients mean weekly attack frequency decreased by 44% after 3 weeks (W-test: $p = 0.03$) and by 34% after 4 weeks (n=6; W-test: $p = 0.04$). Four weeks after the last stimulation, attacks had decreased by 73% (n=5). The first 3 enrolled patients had superficial skin burns under the adhesive cathode electrode. Sponge electrodes were used for all subsequent patients without any adverse effect. This study is ongoing and will include 20 patients.

Conclusion: Anodal tDCS targeting the anterior cingulate gyrus may be promising for the preventive treatment of chronic cluster headache according to the interim results of this ongoing proof-of-concept study. The use of adhesive electrodes is not recommended.

Disclosure: This trial was funded by the Fondation Roi Baudouin. Devices were provided by Cefaly Technology®.

P1229

Thermal pain threshold in migraine: comparison between episodic or chronic migraine patients and healthy volunteers using QST

S.L. Sava, R. Baschi, A. Cosseddu, K. D'Ostilio,
V. De Pasqua, J. Schoenen, D. Magis
Headache Research Unit, Departement of Neurology, Liege, Belgium

Background and aims: Cutaneous allodynia is frequent interictally in migraine, more so in chronic (CM) than in episodic migraine (EM) (Schwedt et al 2011). In this study we assessed thermal pain thresholds with quantitative sensory testing (QST) in healthy volunteers (HV) and episodic (EM) or chronic migraineurs (CM) between attacks.

Methods: Cold and heat sensory (CST & HST) and pain thresholds (CPT & HPT) were measured in 28 HV, 21 EM and 18 CM patients between attacks with a Medoc° Thermal Sensory Analyser. During incrementing or decrementing caloric stimulation with a 5.7 cm^2 probe placed on the forearm or the forehead subjects were asked to press a button when the stimulus was perceived and when it became painful. The means of 3 stimulations were compared between groups with One-Way ANOVA.

Results: There were no significant differences in forehead QST between the 3 groups. By contrast, in the forearm CST was increased in CM (28.35°C) compared to HV (29.72°C) ($p=0.02$; $F=3.73$), while HST was decreased (CM=35.27°C; HV=34.13°C) ($p=0.004$; $F=5.93$) and CPT decreased (CM=19.12°C; HV=12.69°C) ($p=0.02$; $F=3.93$). QST was not different between EM and HV.

Conclusion: Decreased forearm cold pain thresholds suggest that chronic migraine patients have selective extracephalic cold allodynia between attacks. Since forehead thermonociceptive thresholds are normal, this is probably not a consequence of the headache. Whether it might be explained by malfunctioning endogenous pain control or eventually involvement of the cold/menthol sensing TRPM8 receptor, of which the gene is associated with migraine in GWAS, deserves further research.

Disclosure: Nothing to disclose

P1230

Modulation of the nociceptive blink reflex by repetitive transcranial magnetic stimulation in healthy volunteers: comparison of visual or motor cortex stimulation.

S.L. Sava, A. Cosseddu, K. D'Ostilio, V. De Pasqua, J. Schoenen, D. Magis

Headache Research Unit, Departement of Neurology, Liege, Belgium

Background and aims: Connexions between cortex and the trigeminal system may play a role in migraine. Repetitive transcranial magnetic stimulation (rTMS) of visual (Sava et al., 2014) or motor cortex (M1) (De Vito et al. 2009) modulates the trigeminal nociceptive system. In this study we searched which of visual or motor cortex rTMS has the greatest effect.

Methods: Nociception specific blink reflexes (nBR) were recorded in 37 healthy volunteers (HV). rTMS of visual cortex was performed in 22 HV, M1 rTMS in 15 HV. With a figure-of-eight coil 800 pulses were delivered at 1 Hz or 10 Hz in random order on separate days. Before and after rTMS we measured sensory and pain thresholds, R2 area under the curve (AUC) and habituation on 15 averagings partitioned in 3 blocks of 5 responses.

Results: 1 Hz rTMS over visual cortex decreased pain threshold ($p=0.001$), increased R2 AUC of the 1st nBR block bilaterally ($p=0.02$) and increased habituation contralaterally ($p=0.0002$). 10 Hz rTMS over the visual cortex had no effect on nBR.

Over M1, 1 and 10 Hz rTMS increased habituation contralaterally ($p=0.004$ and $p=0.01$ respectively), but had no effect on pain thresholds or nBR amplitude.

Conclusion: Visual rTMS is more effective on trigeminal nociception than M1 rTMS. In HV the visual cortex seems to have stronger functional connexions with the trigeminal nociceptive system than the motor cortex, which may have implications for the use of rTMS to treat trigeminal pain.

Disclosure: Nothing to disclose

P1231

Central sensitisation phenomena in chronic migraine and chronic orofacial Pain

M.D.L.A. Mangas Guijarro[1], A. Gil Martinez[2], S. Lopez Pozo[3], M. Lara Lara[4], E. Díez-Tejedor[5]

[1]La Paz University Hospital. IdiPAZ Health Research Institute , Neurology. Headache Clinic, Madrid, Spain, [2]La Paz University Hospital. CSEU La Salle. Autónoma of Madrid University, Physiotherapy, Madrid, Spain, [3]La Paz University Hospital, Physiotherapy, Madrid, Spain, [4]La Paz University Hospital. IdiPAZ Health Research Institute, Neurology. Headache Clinic, Spain, Spain, [5]Hospital Universitario la Paz, Neurology department and Stroke centerdepartment and Stroke center, Madrid, Spain

Background and aims: Previous studies have suggested the presence of central nociceptive impairment in chronic migraine(CM) and chronic orofacial pain(COP) attributed to temporomandibular disorders(TMD), but available results are conflicting. In addition, some chronic pain comorbidity, such as anxiety or depression are known to affect pain sensitivity. Our aim was to investigate central sensitisation, disability and psychiatric comorbidity in patients with CM and COP attributed to TMD compared to healthy subjects.

Methods: Cross-sectional observational study with 33 subjects suffering from CM, 23 heterogeneous COP and 26 matched healthy controls. Bilateral multi-segmental pressure pain thresholds (PPTs), temporal sumamation of pain (TSP), and information about duration-of-pain history, Neck Disability Index (NDI), Craniofacial Pain Disability Inventory (CF-PDI), Beck Depression Inventory (BDI) and State Trait Anxiety Inventory (STAI) scores were analyzed.

Results: 82 participants (79 women), mean age, 47.2 years (21-70). On average, there were significant differences in PPTs (all sites: $P<0.001$), TSP (all sites: $P<0.009$), NDI ($P<0.001$), CF-PDI ($P<0.001$) and BDI score ($P<0.02$) in patients with CM and COP as compared to healthy controls. Nevertheless, there were no significant differences in the magnitude of PPT decreases, as well as in TSP and BDI between both groups ($P>0.05$). PPT levels over distant pain-free areas were positively correlated to PPTs over trigemino-cervical areas ($P<0.01$). Additionally, positive correlation between duration-of-pain history and TSP was found ($P<0.05$).

Conclusion: The results revealed bilateral widespread pressure pain hypersensitivity in patients with CM and COP attributed to TMD. These findings support the view that central sensitization mechanisms are involved in both conditions.

Disclosure: Nothing to disclose

P1232

Vestibular migraine: clinical characteristics in a series of 24 cases

E. Martínez Velasco[1], M. Ruiz Piñero[1], M. de Lera[2], M. Pedraza[2], A. Juanatey[3], L. Blanco[3], J.A. Cámara-Arnaz[4], J.I. Benito-Orejas[4], A.L. Guerrero[2]

[1]Valladolid, Spain, [2]Valladolid Hospital, Neurology, Valladolid, Spain, [3]Clinic Hospital, Neurology, Valladolid, Spain, [4]Clinic Hospital, Otorhinolaryngology, Valladolid, Spain

Background and aims: Vestibular Migraine (VM) has been included in the appendix of the International Classification of Headache Disorders (ICHD-III). It is defined by vestibular symptoms of moderate to severe intensity, associated with headache with migrainous features, visual aura or photo-phonophobia. We aimed to analyze demographic and clinical characteristics of a series of 24 cases.

Methods: We considered consecutive patients who attended from January 2014 to January 2015 in an outpatient headache office. We gathered age at inclusion, age at onset of migraine and VM, and intensity, duration and characteristics of vestibular symptoms. We excluded patients with other vestibular disorders.

Results: 24 patients (16 females, 8 males) were included. Age at inclusion was 28.8±12.5 years (14-52), at migraine onset 19.2±9.6 (7-46) and at VM onset 24.4±11.1 (7-46). 5 patients (20.8%) fulfilled criteria of chronic migraine. Regarding vestibular symptoms, 2 patients (8.3%) rated them as severe and occurred in 85.4±21.4% (40-100) of migraine attacks. Duration of episodes was quite variable. Vertigo was described as internal in 6 patients (25%), external in 17 (70.8%) and both internal an external in one (4.2%). In 9 cases (37.5%) vertigo was spontaneous, in 20 (83.3%) positional and in 11 (45.8%) motion-induced. No patient described visually induced vertigo or head motion dizziness with nausea. Aural fullness (16.7%) and tinnitus (33.3%) were common accompanying symptoms.

Conclusion: Vestibular migraine diagnosed according to ICHD-III criteria is not uncommon in a headache office. Most frequent vestibular symptoms are spontaneous, positional and motion-induced vertigo.

Disclosure: Nothing to disclose

Movement disorders 3

P1233

Fahr's disease: heterogeneous clinical manifestations of an under-recognized disease

L. Magistrelli[1], M. Carecchio[1], B. Garavaglia[2], A. Stecco[3], C. Barzaghi[4], C. Comi[5], R. Cantello[6]
[1]Novara, Italy, [2]Milan, Italy, [3]Department of Translational Medicine, Section of Radiology, . Department of Translational Medicine, Section of Radiology , Novara, Italy, [4]"C.Besta" Milan, Italy , Molecular Neurogenetics Unit, Milan, Italy, [5]University of Eastern Piedmont, "Amedeo Avogadro", Novara, Italy , Department of Translational Medicine, Section of Neurology, Novara, Italy, [6]Novara, Italy

Background and aims: Fahr's disease (FD) is characterized by intracranial calcifications mainly involving basal ganglia and dentate nuclei. Three causative genes (SLC20A2, PDGFB, PDGFRB) have been discovered so far. Clinical presentation is heterogeneous and sometimes diagnosis may be incidental. Our aim is to define the aetiological, clinical, genetic spectrum of patients with a radiological CT scan consistent with FD.

Methods: We investigated all the reports of CT brain scan performed at the Radiology Department of Maggiore Hospital, Novara, Italy, from 2008 to 2014 using "Fahr" and "basal ganglia calcifications" as keywords. The selected scans were reviewed by an expert neuroradiologist who excluded those not consistent with FD, according to Manyam. Thereafter, we analyzed available clinical and laboratory records. In a few patients, regularly followed-up at the Neurology Department, we also performed genetic analyses.

Results: Out of 194/58000 patients with evidence of cerebral calcifications, only 67 had a CT scan consistent with FD. Secondary causes were ruled out; genetic analysis was performed in 9 patients [Table 1], with mutations in SCL20A2 gene identified in three cases (c.338C>G in a 66-year-old man with focal chorea of the hand, c.1463A>G in a 61-year-old woman with subjective memory complaints, and c.1765G>A in an 82-year-old woman with drowsiness, visual hallucinations and short stature). A PDGFRB mutation (c.676C>T) was detected in a 33-year-old man with paroxysmal kinesigenic dystonia.

Table 1.

Patient	Age	SLC20A2 mutation	Family history	Onset symptoms	CT distribution of calcifications
1	32	Negative (PDGFRB c.676C>T mutation)	Negative	paroxistic kinesigenic dystonia	Caudate, lenticular nuclei, thalamus and dentate nuclei
2	82	c.1765G>A	Positive (nephew)	Visual hallucinations	Lenticular and dentate nuclei
3	69	Negative	Negative	Parkinsonism	Globus pallidus internus
4	61	c.1463A>G	Negative	Memory deficits	Pallidi
5	81	Negative	Negative	Ischemic stroke	Lenticular and dentate nuclei
6	69	Negative	Negative	Parkinsonism	Lenticular and dentate nuclei
7	52	Negative	Positive	Dysarthria	Lenticular nuclei
8	66	c.338C>G	Negative	Distal choreic movements	Putamen, thalamus, caudate and lenticular nuclei
9	77	Negative	Negative	Parkinsonism and dysarthria	Lenticular and dentate nuclei, subcortical white matter.

Characteristics of patients genetically tested

Conclusion: FD can present with different clinical pictures and sometimes diagnosis can be incidental. Some cases may go undiagnosed, making FD more frequent than previously thought.

Disclosure: Nothing to disclose

P1234

Optical coherence tomography in Huntington's disease: a potential biomarker for cognitive decline?

A. Monteiro[1], A. Costa[1], C. Andrade[1], J. Beato[2], S. Penas[2], J. Guimaraes[1], F. Reis[2], C. Garrett[1]
[1]Centro Hospitalar de São João, Neurology, Porto, Portugal, [2]Centro Hospitalar de São João, Ophthalmology, Porto, Portugal

Background and aims: The diagnosis of Huntington's disease (HD) is mostly based on motor manifestations. Cognitive changes, however, are early and debilitating HD manifestations. We have previously studied the correlation of spectral-domain optical coherence tomography (SD-OCT) retinal and choroidal changes with disease stage and severity. The aim of the present study was to investigate their correlation with cognitive status in HD.

Methods: A prospective cross-sectional observational study was performed including 15 eyes of 8 HD patients. Cognition was evaluated using the Verbal Fluency test, the Stroop Color Word Test and Symbol Digit Modality Test. Patients underwent examination using Enhanced Depth Imaging (EDI) SD-OCT. Peripapillary retinal nerve fibre thickness (PRNFL), peripapillary choroidal thickness (PCT), macular and choroidal thickness (MT, CT) and volumes (MV, CV) were evaluated.

Results: Positive correlations were found between verbal fluency and several PRNFL, PCT, MT, MV, CT and CV measures, such as the average ($r=0.629$, $p=0.012$) and temporal ($r=0.609$, $p=0.016$) PRNFL, average PCT ($r=0{\cdot}591$, $p=0{\cdot}020$), superior nasal PCT ($r=0.626$, $p=0.013$), total MV ($r=0.554$, $p=0.032$) and CV ($r=0.549$, $p=0.034$). The Symbol Digit Modality test also positively correlated with several retinal and choroidal measures, such as the superior central ($r=0.849$, $p<0.001$), temporal central ($r=0.794$, $p<0.001$) and inferior central MT ($r=0.850$, $p<0.001$). The same holds true for the STROOP-interference test (example, temporal central MT, $r=0.900$, $p<0.001$) (partial results).

Conclusion: Retinal and choroidal thickness and volume reductions seem to be related with cognitive impairment in HD. These measurements may be useful biomarkers of cognitive decline onset and progression in HD.

Disclosure: Nothing to disclose

P1235

New clinical biomarkers in early Parkinson's Disease (PD): preliminary results of the PRO-DY-GI cohort

C. Moreau[1], A. Delval[2], D. Devos[3], T. Perez[4], N. Danel-Buhl[2], K. Dujardin[5], L. Defebvre[2]
[1]Lille, France, [2]CHRU Lille, Lille, France, [3]Lille Nord de France University, CHRU Lille, Lille, France, Department of Movement Disorders; INSERM U1171; Department of Movement Disorders, Lille, France, [4]CHRU Lille, Lille, France, [5]Inserm, U1171, Troubles cognitifs dégénératifs et vasculaires, Lille, Lille, France

Background and aims: The aim of this prospective study is to identify biomarkers predicting axial symptoms' progression in early PD patients.

Methods and Materials: 67 early and de novo PD patients were successively examined in off drug condition at baseline and after 2 years. All of them displayed less than 3 years of disease evolution since the first symptom; 29 were de novo PD patients and 28 were early PD patients, 10 patients were excluded for diagnosis reasons. Assessments included clinical evaluation (MDS UPDRS 1 to 4), dysarthria evaluation by a speech therapist, gait and rhythm abnormailities evaluations, neuropsychological functions, swallow and respiratory functions assessed by a questionnaire and videofluorography plus functionnal respiratory testings.

Results: Results from the 57 patients revealed that 50% displayed a mild dysarthria, with significant worsening of phonetical realisation after 2 years in men only. Paroxysmal rhythm abnormalities were frequent with freezing of upper or lower limb observed in 63% of the patients for at least one evaluation, and festination in 77% of the patients. Oral festination was only present in 10% of the cases in good correlation with axial/ gait disorders. 60% of the patients displayed asymptomatic oral phase swallowing qualitative abnormalities and 30% displayed abnormal pharyngeal phase with pharyngeal resisuals, none of the patients presented aspiration. Respiratory analysis demonstrated an inspiratory insufficiency in 30% of the patients, with diaphragmatic muscular alteration, unresponsive to phrenic nerve magnetic stimulation.

Conclusion: Here we demonstrated the occurence of asymptomatic clinical axial biomarkers in newly diagnosed PD patients.

Disclosure: DR Moreau acts as scientific advisor for aguettant, Abbvie and Medtronics

P1236

Evaluation of non-motor symptoms in opicapone treated Parkinson's disease patients: results from a double-blind, randomized, placebo-controlled study and open-label extension.

C. Oliveira[1], A. Lees[2], J. Ferreira[3], N. Lopes[1], R. Costa[1], R. Pinto[1], T. Nunes[1], J.F. Rocha[1], P. Soares-da-silva[1]
[1]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal, [2]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [3]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal

Background and aims: Opicapone (OPC) is a novel once-daily peripheral COMT inhibitor shown to be effective in reducing OFF-time in Parkinson's disease (PD) patients with motor fluctuations. Here we report the effect of OPC in non-motor symptoms of PD in patients who enrolled the BIPARK-II study.

Methods: Multinational, 14 to 15-week, double-blind (DB), placebo-controlled study evaluating 2 OPC doses (25 and 50mg), followed by a 1-year open-label (OL) extension where all patients received OPC. OL extension started with 25mg-OPC irrespective of prior DB treatment. One week after, either OPC, levodopa or anti-PD drugs could be adjusted based on individual response. Non-motor symptoms were assessed by the Non-Motor Symptoms Scale (NMSS) at different time points, including baseline, end of DB and end of OL. Statistical analysis at DB endpoint were based on an ANCOVA model.

Results: At baseline the mean NMSS scores were 36.7 for 50mg-OPC and 38.2 for 25mg-OPC and placebo. At the end of the DB period, the NMSS total score slightly improved across OPC and placebo groups, with no significant differences between them (-2.02 for 25mg-OPC, -4.9 for 50mg-OPC and -5.2 for placebo). Numerical differences in favor of OPC were seen for the sleep/fatigue domain. At the OL 1-year endpoint a mean improvement of -4.2 in NMSS total score was still observed. No deterioration of any particular domain was observed.

Conclusion: Treatment with OPC was associated with minimal but generally positive effects on non-motor symptoms of PD. Importantly there was no worsening of dysautonomia, hallucinations or cognitive dysfunction.

Disclosure: Nothing to disclose

P1237

Real time imaging of stomach motility in patients with REM-sleep behavior disorder and denovo Parkinson's disease

E. Paule, T. Hasemann, D. Vadasz, K. Eggert, G. Mayer, S. Knake, W.H. Oertel
Philipps-University, Department of Neurology, Marburg, Germany

Background and aims: Gastrointestinal dysfunction is a frequently observed early non-motor symptom of de novo PD. Neuropathological evidence exists for affection of the enteric system by alpha-synuclein aggregopathy in PD. However it is unclear when this affection starts. We selected gastric motility as indicator for gastrointestinal (dys-)function and focused our investigation on subjects with 1) early motor manifestations of PD (denovo PD) or 2) suffering from RBD, with a risk of >80 % for later developing PD. Data was compared with healthy controls (HC).

Methods: After having a standardized breakfast subjects underwent a gastric MRI to visualize the peristalsis of the gastric wall. MRI videos were analyzed by measuring amplitudes, distances and durations of three peristaltic waves (mean of 3 waves = Δ).We calculated the gastric motility index (GMI) using the formula: Δamplitude x Δdistance/Δtime.

Results: 21 denovo PD subjects, 19 RBD subjects and 21 HCs were studied. Patients with de novo PD had significantly reduced amplitudes ($p<0.001$) and GMI ($p=0.002$) compared to HCs. In patients with RBD there was a trend towards a reduced amplitude ($p=0.071$) as well as towards a lower GMI ($p=0.131$).

Conclusion: Our study shows a disturbed gastric motility visualized by real-time MRI in patients with de novo PD and - to a lesser extent - in patients with likely prodromal PD, i.e. RBD. MRI seems to be a promising method to investigate gastrointestinal dysfunction as an early non-motor symptom in patients with PD and may be also in patients at risk to develop PD.

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P1238

Gait disturbances in patients after methanol intoxication

K. Peterová[1], H. Brozova[1], J. Klempir[1], I. Lišková[1], S. Zakharov[2], D. Pelclová[2], E. Ruzicka[1]

[1]Charles University in Prague, The Department of Neurology, Prague, Czech Republic, [2]Charles University in Prague, Department of Occupational Medicine, Prague, Czech Republic

Background: Methanol intoxication is a severe condition, resulting in visual and neurological impairment. In 2012-2013,121 cases of methanol intoxication were reported in Czech Republic.

Aim: To evaluate gait disturbances after methanol intoxication.

Methods: We investigated 44 patients (9 females, aged 48±SD25years) 3-10 months after methanol intoxication. Examination consisted of Fall Efficiency Scale (FES-I) questionnaire, clinical tests of gait and balance (Timed Up and Go test - TUG, 10 Meter Walking Test – 10MWT, Pull test, Romberg test) and gait analysis on the Gaitrite walkway. Findings were compared with 44 age and sex matched healthy persons.

Results: 29/44(66%) patients reported instability according to FES-I, 2/44(4.5%) had abnormal pull test and 6/44(13.6%) a positive Romberg test. Patients were slower in TUG (8.91±2.05vs.5.65±0.95s, $p<0.001$) and fast 10MWT (3.42±0.69vs.2.55±0.50s, $p<0.05$) compared to controls. On Gaitrite, patients had shorter strides during fast walking (0.85±0.14vs.0.94±0.11m, $p<0.001$) and lower cadence (134.67±12.46vs.148.61±16.13step/min; $p<0.001$). While walking with closed eyes, patients presented wider base (13.15±3.48vs.10.40±3.42cm; $p<0.001$) and longer double support phase (25.43±5.75%vs.22.75±3.57%, $p<0.01$) compared to controls.

Conclusion: 66% of patients after methanol intoxication suffer from instability. They differ in several gait parameters compared to controls, especially while fast walking and with closed eyes. Our findings confirm the toxic effects of methanol metabolites on the nervous system, inducing gait disorders and instability.

Disclosure: Study support: General University Hospital in Prague, RVO-VFN64165 Charles University in Prague, PRVOUK-P26/LF1/4,P25/2, Czech Ministry of Health, NT11190-6/2010, OZS/36/4142/2013).

P1239

Abstract cancelled

P1240

Optimizing effects of botulinum toxin treatment by pre and post injection activity

M. Relja[1], M. Maravic[2]

[1]Zagreb, Croatia, [2]Medical School , Department of Neurology, Zagreb, Croatia

Background and aims: To investigate whether pre and post injection activation program (physiotherapy) during treatment of cervical dystonia (CD) patients with botulinum toxin-type A (ona and rima botulinum toxin; BTX-A) could increase and prolong the duration of clinical benefit.

Methods and patients: A total of 33 patients (20 female, 13 male; age range 23-65 y; disease duration >1year) who had improved significantly to BTX-A treatment during first year of treatment (the last dose of BTX-A was injected at least 5 months before the study) were enrolled into the single-blind, cross-over study. Each patients was injected with previously used effective dose of ona and/or rimabotulinum toxin (BTX-A 100-200 U) CD was assessed using validated scale for CD (TWSTRS, ADL, pain score) every 2 weeks. In addition, patients were asked to contact clinic immediately when they deemed the effect of BTX-A. Only during second injection of BTX-A (second study period) activation of injected muscles (with help of physiotherapist) was performed 15 minutes before and immediately after BTX-A injection (30 minutes daily during 2 weeks post injection). Physical activity protocoil included active stretching to increase muscle activity.

Results: BTX-A was effective in improving CD symptoms during both treatment periods. But the duration of clinical improvement was significantly longer (10-15 days) during second study period when the same BTX-A dose was injected in combination with activation procedure physiotherapy.

Conclusion: Our results indicate that pre and post-injection activation manegement could increase the duration of BTX-A, and that the physiotherapy could prolong the intervals between injections.

Disclosure: Nothing to disclose

Movement disorders 4

P1241

Identification of extreme phenotype of essential tremor: a step toward gene identification

M. Renaud, C. Marcel, G. Rudolf, O. Lagha-Boukbiza, J.-B. Chanson, M. Anheim, C. Tranchant
CHU Strasbourg, Neurologie, Strasbourg, France

Background and aims: Essential tremor (ET) is the most common movement disorder frequently characterized by a family history of ET. We aimed at exploring patients with ET to identify distinct phenotypic subgroups in order to facilitate the identification of genes responsible for ET.

Methods: Between June 2011 and November 2013, 68 consecutive patients suspected with ET were included in the prospective, monocentric study. Following items were collected: family history, age of onset, clinical features, benefit of alcohol and drugs, results of electrophysiological recording.

Results: 68 patients were investigated. 14 patients who were diagnosed with psychogenic (5 patients) or dystonic tremor (9 patients) were excluded. Regarding the 54 patients diagnosed with ET, the mean age of onset was 48 years (6-77), and mean disease duration 15 years (1-55). Mean frequency of upper limbs tremor was 6.3 Hz (3.8-11). Age of onset had a bimodal distribution, consistent with phenotypic subgroups. 29 patients (54%) had a family history of ET. In the group of patients whose age of onset was before 30 years, benefit of alcohol ($p<0.01$) and family history of ET ($p<0.01$) were significantly more frequent and the disease progression was less severe ($p<0.0001$).

Conclusion: Our data support that distinct phenotypic subgroups of ET may be encountered. We recommend to first study separately extreme phenotype of ET, particularly clear autosomal dominant families with early age at onset (< 30 years) and response to alcohol in order to facilitate the identification of genes responsible for ET. Electromyographic recording remains a strong support to distinguish ET from differential diagnosis.

Disclosure: Nothing to disclose

P1242

Interleaving programming in DBS, a better symptom control tool in Parkinson's and dystonia patients

D. Reyes, V. Salanga, T. Khan, N. Galvez-Jimenez
Cleveland Clinic Florida, Pauline Braathen Neurological Center, Weston, USA

Background and aims: Deep brain stimulation (DBS) is a surgical therapeutic option for patients with Parkinson's disease (PD) or dystonia. Interleaving stimulation enables two separate combinations of contacts in the same lead with simultaneous stimulation of two different anatomical areas. To determine clinical improvement by using interleaving programming in patients with PD or dystonia.

Methods: Prospective study involving a series of cases. Patients with PD or dystonia with DBS implanted coming to the clinic were included. The Unified Parkinson Disease Rating Scale (UPDRS) or Dystonia Rating Scale (DRS) were applied to PD or Dystonia patients respectively, while randomly in off stage (off medications and off DBS programming), on single-programming and finally on interleaving mode.

Results: All four patients were male. The PD patients were older than 60 years with UPDRS score of 55 or more during the Off stage. PD patients on DBS interleaving stimulation mode demonstrated an average of 51% clinical improvement on the UPDRS compared to 37% on single- programming. Two of three PD patients demonstrated improvement in their rigidity scores and all had hypokinetic symptoms improvement but no significant improvement in the tremor section. One patient with genetic torsion dystonia on interleaving showed a 54% reduction in the Dystonia Rating Scale. No side effects on the interleaving mode.

Conclusion: Interleaving is a useful tool to control electrical stimulation of a wider region, with a cumulative benefit. STN or Thalamic interleaving programming may provide additional improvement. And favors submaximal amplitude, with a more localized stimulation and a broader anatomical area with less side effects.

Disclosure: Nothing to disclose

P1243

Caffeine exposure and the risk of Parkinson's disease: an update of a systematic review and meta-analysis of observational studies

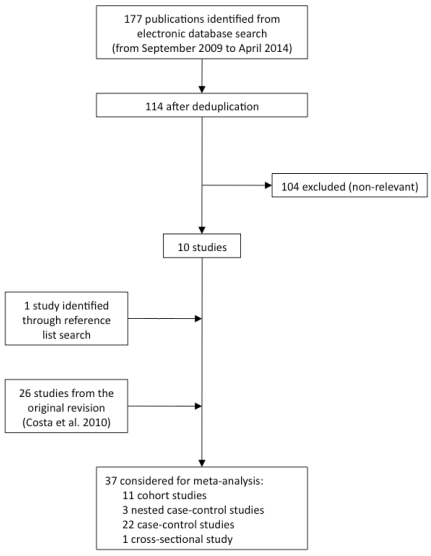
F. Rodrigues, D. Caldeira, J. Ferreira, J. Costa
Instituto de Medicina Molecular, Clinical Pharmacology Unit, Lisbon, Portugal

Background and aims: It is well established – although poorly understood - that a complex and multifactorial relation between genetic and environmental factors takes place in Parkinson's disease (PD). Indeed, PD belongs to the ever-growing group of diseases that occur less frequently in coffee-drinkers.

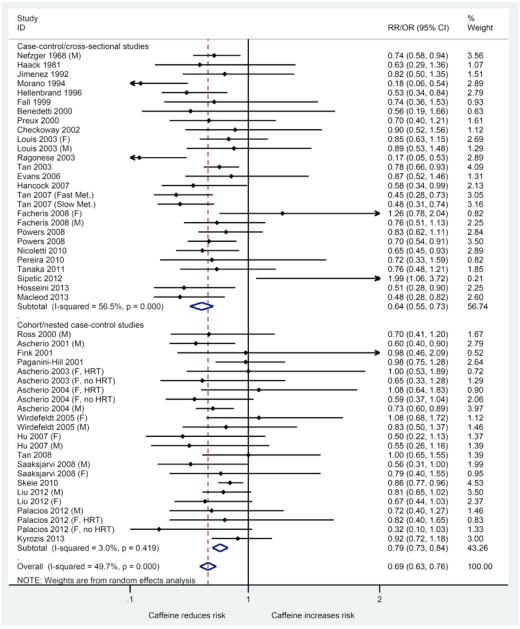
Objectives: To quantify the association between caffeine intake and PD.

Methods: This is an update of a published systematic review and meta-analysis by our group in 2010. Data sources: MEDLINE, Web of Science, EMBASE, LILACS and reference lists, up to April/2014, no restrictions made. Eligibility criteria: observational studies evaluating the relation between exposure to coffee/caffeine and the risk of PD. Study appraisal and synthesis: Authors performed record selection, study screening and data collection independently. Quantitative data synthesis used random-effects meta-analysis. Heterogeneity and publication bias were quantified.

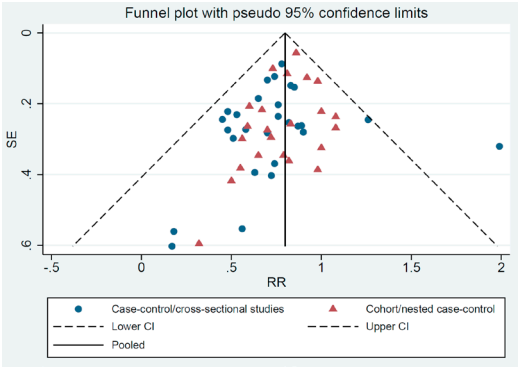
Results: 37 studies were included (figure 1). Caffeine exposure was associated with a 31% reduction in the risk of developing PD (RR:0.69; 95%CI: 0.63 to 0.76, I2=49.7%) (figure 2). Similar results were attained when considering only cohort studies, without the expense of heterogeneity. Risk reduction was found for both men (RR: 0.73, 95%CI: 0.65–0.80, I2=0.0%) and women (RR:0.76, 95%CI: 0.63–0.90, I2=14.9%), as well as for women under hormonal replacement therapy (HRT) (RR:0.67, 95%CI: 0.46–0.88, I2=6.5%). Publication bias was not detected (figure 3).



Flow-chart



Meta-analysis for the association between caffeine and Parkinson's disease



Funnel plot

Conclusion: These results reinforce the inverse association between caffeine intake and PD risk and extend, for the first time, this relationship to women including those undertaking HRT

Disclosure: Nothing to disclose

P1244

Levodopa induced dyskinesias: increased serotonin to dopamine transporter ratios in the putamen of Parkinson's disease patients

A.-A. Roussakis[1], M. Politis[2], D. Towey[3], P. Piccini[1]
[1]Imperial College, Neurology, London, United Kingdom, [2]Kings College Hospital, Neurosciences, London, United Kingdom, [3]Imperial College, Nuclear Medicine, London, United Kingdom

Background and aims: Serotonergic mechanisms play a key role in the development of the Levodopa-induced dyskinesias (LIDs) in patients with Parkinson's disease (PD). We hypothesised that an unfavourable serotonin-to-dopamine terminal ratio in the putamen would be most detrimental in PD patients with dyskinesias. We investigated the role of serotonin (SERT) to dopamine transporter (DAT) binding ratios in the development of LIDs in PD patients.

Methods: 28 patients with advanced PD [17 with LIDs;11 stable] and 12 age and gender-matched healthy controls (HCs) were studied with [11C]DASB PET and [123I]FP-CIT SPECT, which are respective specific markers of DAT and SERT availability in vivo. We have employed a simplified reference tissue model using cerebellar reference for the quantification of [11C]DASB, whereas a semi-quantification approach was used for [123I]FP-CIT. We estimated uptake values in the putamen.

Results: PD patients showed decreases in [123I]FP-CIT binding($p<0.001$) compared to HCs, 51% in the stable and 62% in the LIDs group. PD patients showed decreases in [11C]DASB binding ($p<0.01$), but there were no differences between the stable (37% loss) and LIDs (31% loss) groups. PD patients with LIDs had 103% increased [11C]DASB to [123I]FP-CIT binding ratio, whereas in the PD stable group the ratio was increased by 76%, relative to HCs. Higher [11C]DASB to [123I]FP-CIT binding ratio correlated with longer disease duration for the 28 PD patients ($r=0.52$;$p<0.01$).

Conclusion: SERT to DAT ratio increases as PD progresses and patients experience LIDs. Our findings support the role of serotonin terminals within the dopaminergic denervated striatum for the development of LIDs.

Disclosure: Nothing to disclose

P1245

Evaluation of global impressions of change in opicapone-treated patients with Parkinson's disease and motor fluctuations compared to placebo and entacapone.

A. Santos[1], J. Ferreira[2], A. Lees[3], R. Pinto[1], N. Lopes[1], J.F. Rocha[1], T. Nunes[1], P. Soares-da-Silva[1,4]
[1]BIAL – Portela & Cª – S.A., Dept. R&D, S. Mamede do Coronado, Portugal, [2]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [3]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [4]Department of Pharmacology & Therapeutics fac. of Medicine, University Porto, Portugal

Background and aims: The subject's and investigator's global assessment of change (SGAC and IGAC) are commonly used instruments in clinical trials that provide means for evaluating perceptions about the change in overall condition with treatment.

Methods: Multinational, double-blind, 14- to 15-week, placebo- and active-controlled study (BIPARK I). SGAC and IGAC were secondary efficacy endpoints. SGAC and IGAC were performed in comparison to prior enrolment in the study ("very much improved" to "very much worse"). Both were analysed with a non-parametric van Elteren's test stratified by region.

Results: 590 patients were included in the analysis: placebo (N=120), 5mg-OPC (N=119), 25mg-OPC (N=116), 50mg-OPC (N=115) and entacapone (N=120). The proportion of patients (SGAC) reporting to have "minimally", "much" or "very much improved" ranged between 63.7% to 72.1% for OPC groups vs. 50.9% for placebo and 52.5% for entacapone. The improvement tendency was significant for 25mg-OPC ($p=0.0055$; $p=0.0370$) and 50mg-OPC ($p=0.0008$; $p=0.0091$) compared to placebo and entacapone, respectively. The proportion of patients assessed by investigators (IGAC) as having improved ranged between 60.3% and 73.0% for OPC groups vs. 49.9% for placebo and 50.9% for entacapone. The improvement tendency was significant for 50mg-OPC ($p=0.0005$ and $p=0.0070$ vs. placebo and entacapone, respectively). No tendency was apparent for entacapone when compared to placebo.

Conclusion: OPC was associated with favourable ratings in patient's and clinician's global impressions of change, in contrast to no difference for entacapone compared to placebo in either of these assessments.

Disclosure: Nothing to disclose

P1246

Abstract cancelled

P1247

Improvement of verticality perception after cerebrospinal fluid drainage in idiopathic normal pressure hydrocephalus

C. Selge, R. Schniepp, A. Zwergal, S. Bardins, A. Schepermann, J. Bergmann, K. Jahn
Department of Neurology and German Center for Vertigo and Balance Disorders, Munich, Germany

Background and aims: Idiopathic normal pressure hydrocephalus (iNPH) is a disorder consisting of gait disturbance, cognitive impairment, and urinary symptoms. Most patients show postural imbalance with a tendency to fall backwards. The diagnostic test used to predict whether patients might benefit from shunt surgery is the spinal tap test with drainage of 30 to 50 ml of cerebrospinal fluid (CSF). The aim of our study was to investigate verticality perception in the pitch plane as a possible new method for the evaluation of iNPH.

Methods: A Spacecurl® device was used to measure the subjective postural vertical (SPV) of 20 patients with iNPH (criteria of the International iNPH Guidelines) before and after CSF - drainage. The device was tilted in the sagittal (pitch) and frontal (roll) plane. Blindfolded patients had to indicate the SPV.

Results: Before CSF-drainage patients showed an impaired verticality perception in pitch, with a significant backward deviation of the SPV (mean±SD -3.7±3.6 deg; values of healthy subjects: -1.7 deg to 2.3 deg; pt-test = 0.03). After CSF-drainage patients showed a significant improvement of their verticality perception with normalization of the SPV in the pitch plane (-0.9±1.9 deg; pt-test = 0.001). In the roll plane patients showed no abnormalities before and after CSF-drainage.

Conclusion: The SPV test in pitch shows a reversible altered verticality perception in patients with iNPH. A link between the gait disorder, abnormal verticality perception, and falls in NPH is likely. The SPV might be a promising diagnostic test and prognostic indicator of a positive response to shunt surgery in suspected iNPH.

Disclosure: Nothing to disclose

P1248

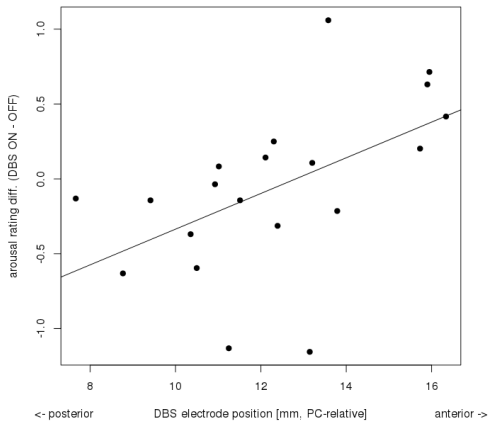
Gradient-like organization of the subthalamic nucleus with respect to emotional arousal: a neuroanatomical study with deep brain stimulation in Parkinson's disease

T. Serranova[1], T. Sieger[2], F. Ruzicka[1], P. Dusek[1], P. Vostatek[3], D. Stastna[4], D. Novak[5], E. Ruzicka[1], D. Urgosik[4], R. Jech[1]
[1]Dept. of Neurology and Center of Clinical Neuroscience, Charles University in Prague, [1]st Faculty of Medicine and General University Hospital, Prague, Czech Republic, [2]Faculty of Electrical Engineering, Czech Technical University, Dept. of Cybernetics, Prague, Czech Republic, [3]Dept. of Cybernetics, Faculty of Electrical Engineering, Czech Technical University, Prague, Dept. of Cybernetics, Faculty of Electrical Engineering, Czech Technical University, Czech Republic, [4]Dept. of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic, [5]Dept. of Cybernetics, Faculty of Electrical Engineering, Czech Technical University, Prague, Czech Republic

Background and aims: Changes in emotional processes have been reported after subthalamic deep brain stimulation (STN-DBS) in Parkinson's disease (PD). Considering the functional organization of the subthalamic nucleus (STN), we hypothesized that STN-DBS might have a differential impact on subjective experience of emotional valence (unpleasantness/pleasantness) and arousal to affective stimuli in relation to the electrode position within the STN.

Methods: 20 PD patients (all men; off-medication) viewed pictures depicting primary rewarding (erotica and food), aversive fearful or neutral stimuli and performed ratings according to emotional valence and arousal in STN-DBS switched ON- and OFF-conditions. The active electrode contact positions in the STN were determined on T1-weighted MRI. The ON vs. OFF ratings differences and their relation to the active contact positions were assessed using linear models.

Results: In the DBS ON-condition, patients attributed lower valence scores to the aversive pictures compared with the OFF-condition ($P < .01$). The active electrode contact position and ON vs. OFF differences in ratings correlated significantly only for arousal but not for valence. Patients with more anteriorly located contacts rated affective pictures as more arousing while patients with more posterior contacts as less arousing in the DBS ON-condition ($P<0.05$).



Correlation between active contact position and ON vs. OFF differences in arousal ratings

Conclusion: While the arousal was systematically influenced by position of the stimulating contact in the STN, the valence of fearful stimuli was shifted towards more negative with the STN-DBS switched on regardless to the electrode position. These results may reflect anterio-posterior gradient of emotional processing in the STN and support functional segregation of valence and arousal at the basal ganglia level.

Disclosure: Nothing to disclose

P1249

Dysphagia in Parkinson's disease: High-risk defining clinical parameters

J.A. Simons[1], N. Eisemann[2], U.M. Fietzek[3], A. Katalinic[4]

[1]University of Luebeck, Institute for Social Medicine and Epidemiology, Lübeck, Germany, [2]University of Luebeck, Institute for Cancer Epidemiology, Lübeck, Germany, [3]Schoen Clinic, Center for Parkinson's Disease and Movement Disorders, Munich, Germany, [4]University of Luebeck, Institute for Social Medicine and Epidemiology, Institute for Cancer Epidemiology, Lübeck, Germany

Background and aims: Dysphagia is a highly relevant symptom in Parkinson's disease (PD). Clinical identification is complex, and often occurs too late with presentation of life-threatening complications, e.g. aspiration pneumonia or malnutrition/dehydration.

Our aim was to define high-risk groups for oropharyngeal dysphagia and laryngeal aspiration using clinical parameters reported to have positive correlation with dysphagia severity in PD.

Methods: Consecutively enrolled PD patients of a German movement disorders center underwent neurological examinations as well as clinical and fiberoptic endoscopic swallowing evaluations. Along the severity grades of underlying rating-scales they were allocated to 3 groups: no dysphagia(A), oropharyngeal dysphagia(B), and dysphagia with penetration/aspiration(C). Cut-off values for high-risk groups (A vs C, or A vs B+C) were determined from ROC curves for modified Hoehn&Yahr scale (HY), UPDRSIII, disease duration, age, drooling score scale, dysarthria score, and body mass index. Relative risks and 95%-confidence intervals were calculated.

Results: The 77 patients (mean age 70.5±8.4, median HY 3) were classified to group A(21), B(34), and C(22). Determined cutoffs were identical for both outcome groups (Figure 1). Dysphagia risk was significantly increased for almost all parameters. Highest clinical relevance was ascertained for UPDRSIII and HY (Table 1).

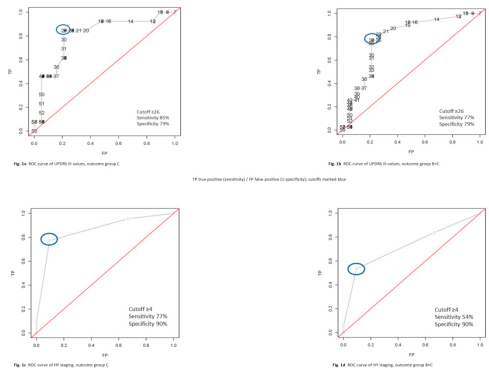


Figure 1 shows the ROC curves for examined outcome groups of these two clinical parameters discovered as strongest risk factors for dysphagia.

Dysphagia outcome	Clinical parameters	Cutoff	RR	95% CI
Group C	UPDRS III	≥ 26	6,23	1.55 – 25.02
	H&Y	≥ 4	4,29	1.90 – 9.73
Group B+C	UPDRS III	≥ 26	2,35	1.37 – 4.05
	H&Y	≥ 4	1,62	1.24 – 2.12

Group C: dysphagia with penetration/aspiration; group B+C: oropharyngeal dysphagia + dysphagia with penetration/aspiration; UPDRS III: Unified Parkinson's Disease Rating Scale, motor part; H&Y: Hoehn & Yahr scale; RR: relative risk, CI: confidence interval

Table 1 shows the relative risks for laryngeal aspiration and/or oropharyngeal dysphagia symptoms for Parkinson's disease patients with the strongest clinical risk factors identified.

Conclusion: Motor performance with UPDRSIII ≥26 and disease stage with HY ≥4 were shown to be high risk factors for dysphagia. In clinical practice patients presenting these cutoffs should be screened for dysphagia with a validated disease-specific questionnaire1 or undergo additional diagnostics.

1. Simons JA, et al.Development and validation of a new screening questionnaire for dysphagia in early stages of Parkinson's disease.ParkinsonismRelatDisord2014;20(9):992–998

Disclosure: Nothing to disclose

MS and related disorders 3

P1250

Representation of dynamic visual stimuli along the visual cortical hierarchy: an fMRI study in optic neuritis patients

T. Benoliel, N. Raz, N. Levin
Hadassah Hebrew University Medical Center , Neurology, Jerusalem, Israel

Background and aims: We had recently suggested that while delayed visual evoked potential (VEP) latencies in the affected eyes (AEs) stem from optic nerve demyelination, latencies in the fellow eyes (FEs) reflect an adaptive process at the cortical level, to compensate for the delayed arrival of visual information via the affected side. The current study is aimed to define the cortical mechanisms that underlie this newly defined adaptive process.

Methods: We studied 13 patients, all of whom had recovered from a single episode of optic neuritis, and 13 matched controls. Visual testing, VEP, and optical coherence tomography were assessed. fMRI examination included dynamic visual functions and retinotopic mapping to define the borders of visual cortical areas.

Results: Reduced activity in early but not in higher visual areas were seen in both the affected and fellow eyes, as compared to controls. When comparing fMRI-signal strength between adjacent visual areas, we found that in the FEs, cortical activation significantly decreased between primary visual cortex (V1) and V2, a decrease which was not found in the AEs or controls. Finally, we showed that inter-eye differences in VEP latencies correlate with cortical activation of the FEs but not the AEs.

Conclusion: The similar cortical activation patterns in the affected and fellow eyes; the decreased in the level of activation between areas V1 and V2 which was seen uniquely in the FEs and the correlation between the cortical activity elicited by the FE and the delta VEP support an early cortical modulatory process in the FE following recovery from optic neuritis.

Disclosure: This study was supported in part by the Sidney and Judy Swartz fund for research in multiple sclerosis.

P1251

Temporal aspects of visual perception in demyelinative diseases

N. Raz, G. Shear-Yeshuv , A. Bick, N. Levin
Hadassah Hebrew University Medical Center , Neurology, Jerusalem, Israel

Background and aims: In chronic optic neuritis patients, timing of signal conduction is specifically affected, thus it stands to reason that temporal vision will be similarly affected.

Herein we assess temporal aspects of visual perception, including temporal resolution and motion perception, and their dependency on conduction velocities, following optic neuritis.

Methods: Critical Flicker fusion frequency (CFFF), two motion perception tasks [object-from-motion (OFM) and number-from-motion (NFM) extraction tasks]; high and low contrast acuities and Visual Evoked Potentials (VEPs) were assessed in 23 optic neuritis patients.

Results: Strong correlations were found between the various dynamic visual function scores. Furthermore, regression models revealed that each of the dynamic visual functions significantly predicted VEP latencies. These findings were specific to patients' affected eyes and were not evident for static visual functions. Fellow eyes' VEP latencies were best predicted by the VEP latencies of the affected eyes.

Conclusion: Delayed signal conduction is functionally manifested as impaired temporal resolution and motion perception. The specificity of these findings to the patients' affected eyes and to dynamic (as opposed to static) visual functions highlights the precision of dynamic visual functions for identifying demyelinative attack. Prolonged VEP latencies in the fellow eyes seem to stem from different patho-physiological processes.

Disclosure: This study was supported in part by the Sidney and Judy Swartz fund for research in multiple sclerosis.

P1252

Rituximab treatment after natalizumab discontinuation in relapsing-remitting multiple sclerosis (RR-MS) patients with high risk of PML

S. Malucchi[1], M. Capobianco[1], M. Malentacchi[1], A. Di Sapio[1], M. Matta[1], A. Oggero[2], M. Lo Re[3], A. Bertolotto[1]

[1]San Luigi Hospital, Multiple Sclerosis Centre, Orbassano, Italy, [2]San Luigi Hospital, Multiple Sclerosis Centre, orbassano, Italy, [3]Dipartimento di Biomedicina Sperimentale e Neuroscienze Clinche, University of Palermo, Palermo, Italy

Background and aims: To evaluate clinical and radiological efficacy of rituximab in RR-MS patients who stop natalizumab treatment.

Patients and methods: 14 MS patients treated with natalizumab for a median number of 42 infusions stopped it for high risk of PML; 10 out of 14 were switched to rituximab, for the impossibility to use alternative drugs; the other 4 received fingolimod and then switched to rituximab due to hepatotoxicity or lack of efficacy. Rituximab (375mg/mq i.v.) was administered every week for 4 weeks; patients underwent monthly CD19 dosage; second infusion was administered in case of disease reactivation or CD19 increase. A wash out period of 2 months from natalizumab suspension was planned; in real practice median wash out period was 3.3 months (1 patient decided to start rituximab after 8 months). Brain MRI was performed in each patient with the same protocol before starting rituximab and then at six and twelve months after it. Median follow up after drug initiation is 11.7 months.

Results: 9 out of 10 patients switching directly from natalizumab to rituximab showed radiological and clinical stability during the wash out period; the patient who started rituximab 8 months after natalizumab withdrawal experienced disease reactivation during the wash out period. Radiological stability was observed at 6 months after rituximab in all the patients and at 12 months in those patients with a follow up one year (5 patients).

Conclusion: The work is in progress but preliminary data suggest that rituximab is a valid therapy after natalizumab discontinuation.

Disclosure: Nothing to disclose

P1253

Does the number of CSF oligoclonal bands have a prognostic role in patients with clinically isolated syndromes?

V. Martinelli[1], G. Passerini[2], G. Dalla Costa[1], M.J. Messina[1], L. Moiola[1], M. Rodegher[1], B. Colombo[1], M. Locatelli[2], G. Comi[1], R. Furlan[3]

[1]San Raffaele Hospital, Neurological Department, Milan, Italy, [2]San Raffaele Hospital, Laboraf, Milan, Italy, [3]San Raffaele Hospital, Neuroimmunological Research Unit, Milan, Italy

Background and aims: The aim of the current study is to evaluate whether the number of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) in patients with clinically isolated syndromes (CIS) adds further information to the already known prognostic factors for conversion to multiple sclerosis (MS).

Methods: A total of 219 patients hospitalized from 2005 to 2012 at San Raffaele Hospital, Italy were included. We evaluated baseline CSF as well as clinical and brain MRI data.

Results: During follow-up (median: 5.04 years) 92 patients (42%) developed clinically definite MS (CDMS). CSF OCBs were present in 153 patients (69.9%), of whom 68 developed subsequently the disease (p 0.05). The number of CSF OCBs further stratified the risk of CDMS: patients with a high number (5-9 and 10-14 CSF OCBs) of CSF OCBs were particularly at risk of CDMS, with more than a 1.5-fold and 2.5-fold increase in risk respectively [HRs (95% CIs): 1.91 (1.06-3.45) and 2.92 (1.33-4.39)], while no further increase in the HRs of disease was observed for patients with a very high number ($\geq$ 15 OCBs) of CSF OCBs. The results did not change after adjusting for the other clinical and MRI covariates.

Conclusion: The number of CSF OCBs has potential prognostic value and could be helpful for clinical decision-making.

Disclosure: Nothing to disclose

P1254

Teriflunomide: pooled hepatic safety outcomes from placebo-controlled studies and long-term extensions

M. Marziniak[1], M.S. Freedman[2], M. Benamor[3], P. Truffinet[3], K. Thangavelu[4], T.P. Leist[5]

[1]kbo-Isar-Amper-Klinikum München-Ost, Haar, Germany, [2]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, Canada, [3]Genzyme, a Sanofi company, Chilly-Mazarin, France, [4]Genzyme, a Sanofi company, Cambridge, USA, [5]Comprehensive Multiple Sclerosis Center, Thomas Jefferson University Hospital, Philadelphia, USA

Background and aims: Elevations of liver enzymes have been observed in patients with relapsing multiple sclerosis who received teriflunomide in clinical trials. Here we report hepatic safety outcomes from teriflunomide clinical trials.

Methods: Two data pools were used: Pool A, placebo-controlled studies (phase 2 [NCT01487096], TEMSO [NCT00134563], TOWER [NCT00751881], TOPIC [NCT00622700]); Pool B, teriflunomide-treated patients (14mg or 7mg) from Pool A and long-term extensions of phase 2 and TEMSO (NCT00228163, NCT00803049). Hepatic assessments included treatment-emergent adverse events (TEAEs) and laboratory parameters. Patients with confirmed alanine aminotransferase (ALT) >3x upper limit of normal were required to discontinue treatment.

Results: In pool A (n=3044), incidence of hepatic TEAEs was higher in teriflunomide groups (14mg, 21.5%; 7mg, 19.8%; placebo, 15.2%), mainly due to asymptomatic ALT increase. Incidence of serious hepatic TEAEs was low and similar across groups (14mg, 2.2%; 7mg, 2.1%; placebo, 2.7%), as was discontinuation due to hepatic TEAEs (14mg, 4.2%; 7mg, 4.5%; placebo, 3.9%). 8 patients (14mg, 2; 7mg, 1; placebo, 5) experienced ALT and bilirubin elevations consistent with Hy's law; all had potential alternative explanations. Most ALT increases occurred within 6 months of treatment initiation, were mild or moderate, and usually resolved without corrective treatment. Similar trends were observed in Pool B (n=2338): 3.5% patients experienced serious hepatic TEAEs and 6% patients discontinued treatment due to hepatic TEAEs over up to 6 years' follow-up.

Conclusion: This pooled analysis was consistent with the individual teriflunomide studies and no new or unexpected hepatic safety signal was identified. Nonetheless, precautionary hepatic monitoring is required as per local labelling.

Disclosure: Study supported by Genzyme, a Sanofi company.

P1255

The potential role of gut immunity in multiple sclerosis

M.J. Messina[1], M. Falcone[2], A. Mariani[3], C. Sorini[2], P.A. Testoni[3], G. Comi[1], V. Martinelli[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [2]Diabetes Research Institute, IRCCS San Raffaele Scientific Institute, Division of Immunology, Transplantation and Infectious Diseases, Milan, Italy, [3]IRCCS San Raffaele Scientific Institute - Vita Salute San Raffaele University, Gastroenterology and Gastrointestinal Endoscopy Unit, Division of Experimental Oncology, Milan, Italy

Background and aims: Several lines of evidence in animal models of Multiple Sclerosis (EAE) indicate that gut immunity is instrumental to maintain immune tolerance towards self-tissues also at sites distal to the intestine. Some environmental factors (diet etc.) seem to increase the risk to develop Multiple Sclerosis (MS) in genetically-at risk individuals by altering gut immunity. The aim of our study is to assess the potential role of gut immunity in MS pathogenesis.

Methods: So far we analyzed gut immune cell subsets in peripheral blood (PBMC) and intestinal mucosal samples isolated from 20 Relapsing-Remitting (RR) patients and age and sex-matched healthy controls who underwent esophago-gastro-duodenal endoscopy (EGDS) for diagnostic purposes. All MS patients had not received corticosteroid treatment in the six months before the EGDS.

Results: We found that effector Th17 cells that play a crucial role in the pathogenesis of experimental models of MS, are present in the intestinal mucosa but not in PBMC. Importantly, MS patients showed an increased Th17/FoxP3+Treg cell ratio compared to healthy controls, indicating a preferential differentiation of effector Th17 cells in their gut mucosa.

Conclusion: Although our data are preliminary, they suggest a specific immune cell defect of the Treg/Th17 balance in the intestinal mucosa of MS patients. They validate previous reports in EAE and provide the first evidence that gut immunity modulate MS pathogenesis in humans. Our next goal is to determine whether microbiota composition is responsible for the alterations of gut immunity and altered Treg/Th17 cell balance in MS patients.

Disclosure: Nothing to disclose

P1256

The Framingham cardiovascular risk score in multiple sclerosis

M. Moccia[1], R. Lanzillo[1], R. Palladino[2], G.T. Maniscalco[1], A. De Rosa[1], C.V. Russo[1], M. Massarelli[1], A. Carotenuto[1], E. Postiglione[1], O. Caporale[2], M. Triassi[2], V. Brescia Morra[1]
[1]Federico II University, Naples, Italy, Department of Neurosciences, Reproductive Science and Odontostomatology, , Naples, Italy, [2]Federico II University, Department of Public Health, Naples, Italy

Background and aims: Some cardiovascular risk factors have been suggested to raise the risk of multiple sclerosis (MS), and to modify its course. However, such factors possibly interact, thus determining a global cardiovascular risk. We aim to compare the global cardiovascular risk of subjects with and without MS by the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR), and to evaluate its importance on MS-related outcomes.
Methods: Age, gender, smoking status, body mass index (BMI), systolic blood pressure, type II diabetes, and use of antihypertensive medications have been recorded in subjects with and without MS to estimate the FR, an individualised percentage risk score estimating the 10-year likelihood of cardiovascular events.
Results: We identified 265 MS subjects, and matched 530 controls at the "Federico II" University Hospital, Naples, Italy. T-test showed similar FR in cases and controls ($p=0.212$), however secondary progressive MS presented significantly higher FR when compared to relapsing remitting MS ($p<0.001$). Linear regression analysis showed a direct relationship between FR and Expanded Disability Status Scale (EDSS) ($p<0.001$) and MS Severity Scale (MSSS) ($p<0.001$).
Conclusion: The FR, evaluating the global cardiovascular health by the interaction among different risk factors, relates to MS disability, severity and course.
Disclosure: Nothing to disclose

P1257

Detection of intrathecal inflammation: CSF reference values for immunoglobulin free light chains (FLC)

F. Mojib-Yezdani, M. Senel, H. Tumani
University of Ulm, Neurology , Ulm, Germany

Background and aims: Oligoclonal bands (OCB) or IgG-index are the most widely used CSF test to detect intrathecal IgG synthesis. However, determination of OCB is non-quantitative and demands methodological expertise. The quantitative IgG-index is associated with a sensitivity lower than that of OCB. Several studies indicated that elevated kappa free light chains (KFLC) and lambda free light chains (LFLC) in CSF might offer a quantitative tool for detection of intrathecal humoral inflammation by avoiding aforementioned limitations of OCB and IgG-index. We aimed to determine CSF reference values for KFLC and LFLC to evaluate their diagnostic relevance in multiple sclerosis (MS) and pathogen-related CNS diseases.
Methods: Paired CSF and serum samples (n=1459) from the Department of Neurology, University of Ulm (Germany) were analyzed prospectively over a period of 1.5 years including n=1039 samples from patients with non-inflammatory neurological diseases (NIND). KFLC, LFLC, Albumin, IgG and lactate were measured by automated nephelometry. OCB were detected by isoelectric focusing (IEF) followed by immunoblotting.
Results: CSF-serum ratios of KFLC (Q KFLC) were plotted against the respective ratios of albumin. The upper 97.5% confidence interval are shown as the approximately upper reference values indicated in figure 1a for Q KFLC and figure 1b for Q LFLC. Data from patients with MS are evaluated based on these albumin ratio related reference range and compared to previously published results.

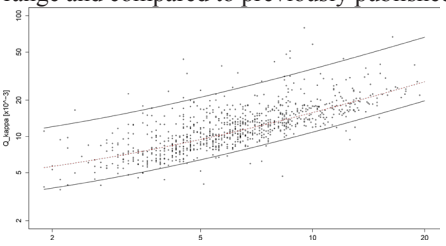


figure 1a

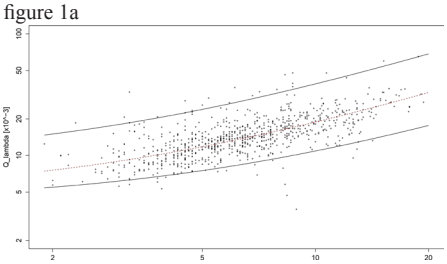


figure 1b

Conclusion: CSF FLC is a rapid and easy to standardize tool to detect intrathecal humoral inflammation and to improve performance of OCB and IgG-index in the context of MS diagnostics.
Disclosure: Nothing to disclose

P1258

Abstract cancelled

Muscle and neuromuscular junction disease 1

P1259

Very late-onset myasthenia gravis in Slovak Republic

I. Martinka[1], J. Bednarik[2], M. Soskova[1], K. Sitarova[1], P. Spalek[1]

[1]*University Hospital Bratislava, Department of Neurology, Bratislava, Slovakia,* [2]*University Hospital Brno, Department of Neurology, Brno, Czech Republic*

Background and aims: Recently there has been an increase in the incidence of myasthenia gravis (MG) in patients over 70 years. The objective of this study is to analyze the clinical features and basic epidemiologic parameters in patients with very late-onset MG (VLOMG) >70 years in Slovakia.

Methods: We reviewed 1950 MG patients from 1978 to 2014. The method of research was to review medical records. We analyzed age at onset, sex, clinical symptoms, presence of thymoma, anti-AChR and anti-MuSK antibodies and basic epidemiologic parameters.

Results: We observed VLOMG in 355 patients (18.2%). Prevalence of VLOMG was 29.5/1 million inhabitants on 31st Dec. 2014. The average annual incidence of VLOMG for the last 10 years is 3.8 /1 million population. Out of the 355 patients, 183 are women (51.6%) and 172 men (48.4%). The mean age at onset was 75.2 years, women 75.7, men 74.5. MG presented initially with ocular symptoms in 73 patients (20.7%), bulbar muscle weakness was present at onset in 161 patients (45.3%). 12 patients (3.4%) had MG associated with thymoma. Autoantibodies were investigated in 298 patients. 279 patients (93.6%) have AChR-positive MG, 2 patients (0.7%) MuSK-positive MG, 17 patients (5.7%) have double-seronegative MG.

Conclusion: VLOMG occurs in 18% of all patients with MG in Slovakia, with slight predominance of women. In VLOMG patients dominates AChR-positivity (93.6%) and predominantly bulbar muscle weakness at onset.

Disclosure: Nothing to disclose

P1260

From the experience of the Italian National Registry a novel tool to dissect the phenotypic complexity of facioscapulohumeral muscular dystrophy: the comprehensive clinical evaluation form

T. Mongini[1], G. Ricci[2], L. Vercelli[1], L. Ruggiero[3], F. Sera[4], A. Nikolic[5], M. Govi[5], F. Mele[5], L. Villa[6], L. Maggi[7], M. Cao[8], M.C. D'Amico[9], G. Siciliano[2], G. Antonini[10], A. Berardinelli[11], L. Santoro[3], M. Moggio[6], L. Morandi[7], E. Pegoraro[8], C. Angelini[12], A. Di Muzio[9], E. Ricci[13], C. Rodolico[14], G. Tomelleri[15], R. Tupler[5]

[1]*University of Torino, Italy, Department of Neurosciences "Rita Levi Montalcini", Turin,* [2]*University of Pisa, Pisa, Italy, Department of Clinical and Experimental Medicine, Neurological Clinic, Pisa,* [3]*University Federico II, Department of Neurosciences and Reproductive and Odontostomatologic Sciences, Naples, Italy,* [4]*UCL Institute of Child Health, MRC Centre of Epidemiology for Child Health, London, United Kingdom,* [5]*Institute of Biology, University of Modena and Reggio Emilia, Modena, Department of Science of Life, Modena,* [6]*IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan,* [7]*Foundation Neurological Institute Carlo Besta, Milan,* [8]*Department of Neurosciences, University of Padua, Padua, Italy, Padua,* [9]*Ospedale Chieti, Dept di Neuroscience, Imaging and Medical sciences , Chieti,* [10]*Department of Neurology, S. Andrea Hospital, Mental Health and Sensory Organs (NESMOS), University of Rome 'sapienza', Rome, Italy, Rome,* [11]*C.Mondino National Neurological Institute, Pavia,* [12]*IRCCS S.Camillo, Lido di Venezia, Italy, Padua,* [13]*Rome,* [14]*AOU Policlinico, Neurosciences, Messina,* [15]*University of Verona, Department of Neurological and Movement Sciences, Verona, Italy*

Background and aims: For the last 20 years, the diagnosis of facioscapulohumeral muscular dystrophy (FSHD) has been confirmed by the detection of one D4Z4 allele with a reduced number (≤ 8) of repeats at 4q35. In the meantime, several atypical phenotypes have been observed among D4Z4 reduced allele (DRA) carriers sometimes with unexpected mode of inheritance. In some cases the high frequency of FSHD molecular signature, also detected in healthy individuals and in asymptomatic relatives of probands, might have influenced diagnosis because of a biased correlation between a generic 'myopathic' phenotype and the detection of a DRA. There is therefore the need to generate tools that support diagnosis and genetic counseling in FSHD.

Methods: The Italian Clinical Network developed the first FSHD clinical form in 2009; since then we systematically analyzed distribution of muscle impairment in over 500 index cases and 300 families and populate the Italian National Registry for FSHD (INRF) with standardized clinical information on certified FSHD patients and families. Based on our six-year experience, we designed and validated a Comprehensive Clinical Evaluation Form (CCEF), defining phenotypic categories by the combination of different clinical features.

Results: Through the CCEF we classify: category A, subjects with typical FSHD phenotype; category B, subjects with incomplete FSHD phenotype; category C, asymptomatic subjects, and category D, myopathic subjects without typic FSHD features.
Conclusion: We propose the widespread use of CCEF to ameliorate the classification of patients and families, to generate information to unravel the genetic complexity of FSHD, and to serve as a major tool for trial readiness.
Disclosure: Supported by Telethon Italy, Grant GUP13012,

P1261

Natural history of sarcoglycanopathies: analysis of 74 Moroccan families.

G.A. Mpandzou, N. Birouk, L. Errguig , H. Belaidi, R. Ouazzani
Centre hospitalier Ibn Sina – Université Mohamed V – Souissi, Service de neurophysiologie clinique, Rabat, Morocco

Background and aims: Sarcoglycanopathies (SG) are autosomal recessive progressive limb-girdle muscular dystrophies (LGMD), due to α-, β-, γ- and δ-sarcoglycan gene mutations, respectively leading to LGMD2D, E, C and F. In North Africa, γ-SG is the most common. The disease progression is highlighted by analysing 82 patients from 74 Moroccan families.
Methods: Throughout a 21-year time lapse, 82 patients were regularly followed-up during an average of 3.7±2.9 years (SD) [Min:Max; 1-13]. The SG diagnosis was established from protein immunostaining on muscle biopsy (97.6%) and/or mutational analysis. Disease progression was assessed annually using two functional scores, muscle strength, climbing stairs and walking perimeter. Clinical and paraclinical characteristics were reported to age at onset.
Results: γ-SG was diagnosed in 80 patients and α-SG in two cases. Consanguinity rate was 68.3% and age at onset, 7.1±2.9 years [1-19]. Difficulty to walk appeared after 1.6±3 years [0-17], and loss of ambulation after 7.3±4.6 years [2-22]. Reduction in respiratory functional vital capacity below 50% was found in ten patients at 21.5±9.4 years of age [11-43]. Five patients suffered from cardiac function impairment with decrease of left ventricular ejection fraction at 25±12.5 years of age [14-45], eight patients from cardiomyopathy at 19±12 years of age [8-45].
Conclusion: The analysis of SG natural history highlights disease prognosis and can thus help in anticipating medical management to improve patient's quality of life.
Disclosure: Nothing to disclose

P1262

A complex phenotype characterized by epilepsy, movement disorders, mental retardation and exercise-induced myoglobinuria caused by two different rare disorders

O. Musumeci[1], E. Ferlazzo[2], G. Annesi[3], S. Romeo[1], C. Rodolico[1], U. Aguglia[4], A. Toscano[1]
[1]University of Messina, Messina, Italy, [2]University Magna Grecia, Catanzaro, Italy, [3]CNR, Cosenza, Italy, [4]Reggio Calabria, Reggio Calabria, Italy

Background and aims: GLUT-1 Deficiency Syndrome (DS) is a rare encephalopathy, caused by impaired glucose transport into the brain, usually presenting with early-onset epilepsy, movement disorders, developmental delay and microcephaly; rhabdomyolysis has never been observed in such patients.

Case Report: We report a 44-year-old man, who presented, since the age of 20, recurrent episodes of rhabdomyolysis after exercise or prolonged fasting; he also showed a mild mental retardation and sporadic choreo-athetoid movements. His 14-year-old son had a psychomotor developmental delay with episodes of drowsiness, head drop and choreo-athetoid movements occurring mainly at fasting or after physical exercise. Neurological examination revealed microcephaly, mild spastic ataxia and mental retardation.
EEG was normal in the proband but in the son showed, during fasting, diffuse spike-wave discharges disappearing after food intake. Brain MRI was normal in both. CSF analysis revealed hypoglycorrhachia (40 mg/dl) in the son.

Results: Clinical and laboratory findings suggested to search for mutations in SCL2A1 (GLUT-1) that revealed an heterozygous mutation (R333W) in both confirming the diagnosis of DS. To better define the recurrent exercise-induced rhabdomyolysis in the father, a forearm ischemic test (normal), EMG (myopathic pattern) and muscle biopsy (unspecific changes) were performed. After having excluded common metabolic causes of recurrent rhabdomyolysis, VLCAD gene analysis in the father showed two known heterozygous mutations (p.G185S and p.R385W) whereas the son carried only the p.G185S.

Conclusion: In conclusion our data evidenced a case of "double trouble" suggesting that, when a known phenotype is accompanied by some atypical features, an alternative explanation of unusual presentations is required

Disclosure: Nothing to disclose

P1263

Echocardiography in patients with myotonic dystrophy type 1

S.Z. Peric, T. Paunic, V. Dobricic, I. Novakovic, I. Basta, D. Lavrnic, V. Rakocevic-Stojanovic
Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia

Background and aims: To analyze results of echocardiographic examination in a large cohort of patients with myotonic dystrophy type 1 (DM1).

Methods: During an 8-year period study comprised 111 genetically confirmed DM1 patients (45% males, aged 42.2±10.9 years, mean Muscular Impairment Rating Scale 3.3±1.1) that were examined using echocardiography during their first hospitalization at the Neurology Clinic. They were matched for gender and age with 71 healthy controls (HCs).

Results: Dilatative cardiomyopathy was observed in 4.5% of DM1 patients and in no one of HCs ($p>0.05$), with similar ejection fraction of the left ventricle in both groups of subjects (61.3±7.5% vs. 62.2±3.4%, $p>0.05$). Decreased contractility and impaired kinetics of the left ventricle were more frequent in DM1 patients compared to HCs (6.3% vs. 0.0%, $p<0.05$ and 9.7% vs. 0.0%, $p<0.01$). DM1 patients also had lower maximal mitral velocity (0.83±0.09 vs. 0.88±0.08, $p<0.01$) and higher percentage of the mitral valve prolapse (23.0% vs. 8.5%, $p<0.05$). On the other hand, tricuspid valve fibrosis (12.7% vs. 0.0%, $p<0.01$) and aortic regurgitation were even more common in HCs (9.9% vs. 1.8%, $p<0.05$). Other echocardiographic parameters did not differ between groups.

Conclusion: Our study showed mild impairments of the heart structure and dynamics in DM1 patients. Dilatative cardiomyopathy was registered in less than 5% of patients. We found impaired left ventricle kinetics and mitral valve prolapse to be more common in DM1 than in HCs.

Disclosure: Nothing to disclose

P1264

Multiple deletions in mitochondrial DNA in myofibrillar myopathy and centronuclear myopathy

J. Schäfer, U. Reuner, H. Reichmann, M. Meinhardt, S. Jackson

Dept. of Neurology, Dresden, Germany

Background and aims: Multiple deletions in mitochondrial DNA (mtDNA) are associated with mutations in nuclear genes which encode proteins either directly or indirectly involved in the replication or maintenance of mtDNA. To date, mutations in twelve nuclear genes, POLG, POLG2, C10orf2, SLC25A4, RRM2B, TK2, MPV17, DGUOK, OPA1, MFN2, MGME1, and DNA2 have been identified in patients with multiple deletions in mtDNA.

Mitochondrial changes have also been identified in skeletal muscle from patients with myofibrillar myopathy, with histochemical changes such as rubbed out fibres observed with COX and NADH staining, and focal clustering and depletion of mitochondria. Mitochondrial pathology, including COX negative and ragged red fibres, and paracrystalline inclusions have also been described in patients with centronuclear myopathy due to mutations in DNM2, which encodes Dynamin 2, a GTPase which is involved in membrane trafficking.

Methods: We describe our clinical, histological and molecular genetic findings in two patients with multiple mtDNA deletions.

Results: In one patient, a 70-year-old male who presented with a history of exercise induced muscle pain and distal myopathy we identified a novel pArg2364His mutation in the gene FLNC which encodes the actin binding protein filamin-C. In the second patient, a 40-year-old male who presented at age 3 with ataxia and later developed facial myopathy, proximal muscle weakness, and CPEO, histochemical investigation indicated centronuclear myopathy, and a p.Glu560Lys mutation in DNM2 was identified.

Conclusion: Our findings suggest that FLNC and DNM2 should be added to the list of genes associated with multiple deletions in mtDNA

Disclosure: Nothing to disclose

P1265

Muscle MRI in sarcoglycanopathies

G. Tasca[1], M. Monforte[1], G. Brisca[2], A.D'Amico[3], J. Díaz-Manera[4], L. Maggi[5], N. Al Shaik[6], A. Pichiecchio[7], A. Berardinelli[7], N. Løkken[8], F. Munell[9], A. Sanchez[9], L. Morandi[5], N. Voermans[10], J. Dastgir[11], M.C. Walter[12], C. Bönnemann[13], V. Straub[14], S. Quijano-Roy[15], R. Carlier[15], J. Vissing[16], E. Mercuri[17], F. Muntoni[18], E. Ricci[1], E. Bertini[1], B. Udd[19], C. Bruno[2]

[1]Rome, Italy, [2]IRCCS Giannina Gaslini, Genoa, Italy, [3]Bambino Gesù Children's Research Hospital, Rome, Italy, [4]Barcelona, Spain, [5]Foundation Neurological Institute Carlo Besta, Milan, Italy, [6]Dubowitz Neuromuscular Centre, Institute of Child Health, London, United Kingdom, [7]C.Mondino National Neurological Institute, Pavia, Italy, [8]Rigshospitalet, University of Copenhaegn, Copenhagen, Denmark, [9]Vall d'Hebrón University Hospital, Barcelona, Spain, [10]NIJMEGEN (GLD), The Netherlands, [11]National Institute of Neurological Disorders and Stroke/NIH, Bethesda, USA, [12]Munich, Germany, [13]Bethesda, , [14]Newcastle upon Tyne, , [15]Hôpital Raymond Poincaré, Garches, France, [16]Copenhagen, [17]Catholic University School of Medicine, Rome, Italy, [18]London, UK, [19]Tampere, Finland

Introduction: Sarcoglycanopathies (LGMD2C-2F) are Limb-Girdle Muscular Dystrophies caused by mutations in one of the four genes encoding for muscle sarcoglycans. The objective of this study is to characterize the pattern and spectrum of MRI involvement in a large cohort of patients with sarcoglycanopathy.

Methods: Lower limb MRI scans of LGMD2C-2F patients were collected in multiple neuromuscular referral centers in Europe and USA, ranging from severe childhood variants to milder adult onset forms. Muscle involvement was evaluated semiquantitatively on T1-weighted images according to a visual score, and the global pattern was assessed as well.

Results: A common pattern of involvement was found in all the sarcoglycanopathies irrespective of the mutated gene. The most and earliest affected muscles were the adductors, glutei and posterior thigh groups, while lower leg muscles were relatively spared even in advanced disease.

Conclusion: Muscle involvement on MRI is consistent in LGMD2C-F patients and some clues can be helpful in distinguishing sarcoglycanopathies from other LGMDs or dystrophinopathies, which represent the most common differential diagnoses. Muscle MRI can also provide insights about progressive involvement of the different muscles over time as well as about selective susceptibility or resistance of specific muscles when one of the sarcoglycans is deficient.

Disclosure: Nothing to disclose

Neuroepidemiology

P1266

Traumatic events and amyotrophic lateral sclerosis: a European case-control study

E. Beghi, E. Pupillo, P. Messina, #&. EURALS Consortium
IRCCS - Istituto Mario Negri, Neuroscience, Milan, Italy

Background and aims: An Italian study on the association between amyotrophic lateral sclerosis (ALS) and trauma found that antecedent, repeated and severe trauma may be risk factors for ALS. These data required replication in other countries.

Methods: A case–control study was undertaken in Italy, France, England, Ireland, and Serbia. Cases were patients with newly diagnosed ALS from seven population-based registries. For each case, two controls were selected from the general practitioners' lists, matched for age, sex, and residency. Traumatic events occurred 5+ years before ALS onset were recorded with details on type, site, timing, severity, and complications. The risks were assessed as odds ratios (ORs) with 95% confidence intervals (CI), crude and adjusted for age, sex, education, interviewee (patient or surrogate), physical activity, BMI, smoking, alcohol, and coffee.

Results: 575 patients and 1150 controls were enrolled. One or more traumatic events were reported by 28.7% of cases and 27.83% (OR 1.10; 95%CI 0.87–1.39). The ORs was 1.34 (95%CI 1.04–1.72) for moderate traumatic events, 1.54 (95%CI 1.24–1.92) for traumatic events leading to disability and 2.94 (95%CI 1.25–6.92) for 2+ traumatic brain injury (TBI).

Conclusion: Moderate to severe traumatic events and repeated TBI are risk factors for ALS.

Disclosure: Study supported by the American ALS Association (grant 1524).

P1267

ALS and cancer: is there a link?

D. Bertuzzo[1], A. Calvo[2], C. Moglia[2], S. Cammarosano[3], U. Manera[2], I. Antonio[1], F. Pisano[4], G. Mora[5], E. Bottacchi[6], L. Mazzini[7], E. Bersano[7], M.C. Vigliani[8], A. Chiò[1]
[1]Amyotrophic Lateral Sclerosis Center, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, [2]Amyotrophic Lateral Sclerosis Center, University of Turin, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, [3]Amyotrophic Lateral Sclerosis Center, Rita Levi Montalcini Department of Neuroscience, Amyotrophic Lateral Sclerosis Center, Amyotrophic Lateral Sclerosis Center, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, [4]Salvatore Maugeri Foundation, Istituto Di Ricovero e Cura a Carattere Scientifico, Scientific Institute of Veruno, Veruno, Italy, [5]Fondazione Maugeri, Neurorehabilitation, Milan, Italy, [6]Department of Neurology, Azienda Ospedaliera Regionale di Aosta, Azienda Unità Sanitaria Locale Valle d'Aosta, Aosta, Italy, [7]Amyotrophic Lateral Sclerosis Center, Department of Neurology, Azienda Ospedaliero Universitaria Maggiore di Novara, Novara, Italy, [8]Neuroscience Institute of Torino, Turin, Italy

Background and aims: We investigated whether patients with ALS have a higher than expected incidence of cancer and how the co-occurrence of cancer modifies ALS prognosis

Methods: The study population were the 1260 ALS cases incident in Piemonte and Valle d'Aosta in the period 1995-2004. Only patients with cancers occurring in the 6 months before or after the onset of ALS were included (46 patients). The odds ratio of having a cancer was calculated using as reference the incidence rate of cancers in the same area for the period 2004-2006 (Cancer Registry of Piemonte Region). Odds ratio was calculated by gender and 5-year age-classes.

Results: Cancer in ALS was significantly more frequent than expected in both genders (men, OR 2,01; 99% c.i.1.15-3.28; women 3.43; 1.78-5.95). The excess of cancers was mostly due to lung cancers (men 4.35, 1.51-9.68; women 4.83, 0.58-14.97) and to breast cancers (6.16, 2.29-13.18). Patients with cancer had a significantly shorter survival than those without cancer (p=0.01); this difference was mainly due to patients with lung cancer.

Conclusion: Cancers, predominantly lung and breast cancers, have an incidence significantly higher than expected in ALS population. Patients with cancer have a worse clinical progression than patients without cancer.

Disclosure: Nothing to disclose

P1268

Do arterial hypertension and diabetes modify ALS phenotype and outcome? A population-based study

D. Bertuzzo[1], A. Calvo[1], C. Moglia[1], A. Canosa[1], S. Cammarosano[2], A. Ilardi[1], U. Manera[1], P. Cugnasco[3], E. Bersano[4], S. De Mercanti[5], K. Marinou[6], E. Bottacchi[7], F. Pisano[8], R. Cantello[9], L. Mazzini[4], G. Mora[10], A. Chiò[1]

[1]Amyotrophic Lateral Sclerosis Center, University of Turin, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, [2]Amyotrophic Lateral Sclerosis Center, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, Italy, [3]Amyotrophic Lateral Sclerosis Center, Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, Italy, [4]Amyotrophic Lateral Sclerosis Center, Department of Neurology, Azienda Ospedaliero Universitaria Maggiore di Novara, Novara, Italy, [5]Department of Biological and Clinical Science, University of Turin, and Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano (TO), Turin, [6]Salvatore Maugeri Foundation, IRCSS, Scientific Institute of Milano, Milan, Italy, [7]Department of Neurology, Azienda Ospedaliera Regionale di Aosta, Azienda Unità Sanitaria Locale Valle d'Aosta, Aosta, Italy, [8]Salvatore Maugeri Foundation, Istituto Di Ricovero e Cura a Carattere Scientifico, Scientific Institute of Veruno, Veruno, Italy, [9]NOVARA, Italy, [10]Fondazione Maugeri, Neurorehabilitation, Milan, Italy

Background and aims: Several studies have assessed vascular risk factors in ALS. It has been reported that pre-morbid AH shortens the survival in ALS patients while diabetes mellitus type II (DM) delays the onset of motor symptoms

Methods: We include all the 712 ALS patients incident in the period 2007-2011 in Piemonte region (323 women and 389 men, mean age at onset 66.7 years [SD 10.7]) and retrospectively investigate the presence of AH and DM.

Results: Of the 712 patients, 314 (44.1%) had AH for at least 2 years before the onset of ALS, and 68 (9.6%) had DM. Patients with AH were significantly older (men, 68.4 [9.0] vs. 64.8 [11.4]; women 70.4 [8.5] vs. 64.0 [11.6]; p=0.0001 for both). Pre-morbid AH or DM did not influence the site of onset of ALS (bulbar vs. spinal). The mean age at onset did not differ between patients with and without DM (men, 67.9 [8.8] vs. 66.1 [10.8]; women, 68.7 [8.7] vs. 66.9 [10.9]; p=n.s. for both). Survival from onset was reduced in women (p=0.05) but not in men with AH, and was not affected by the presence of DM

Conclusion: The presence of pre-morbid AH or DM did not influence neither phenotype nor survival of ALS patients

Disclosure: Nothing to disclose

P1269

Prevalence of stroke symptoms among stroke-free residents: national data from Lebanon

R. Farah[1], R. K. Zeidan[2], M. Chahine[3], R. Chahine[3], P. Salameh[4], H. Hosseini[1]

[1]Henri Mondor Hospital, Neurology , Paris, France, [2]Ecole Doctorale Biologie Santé Biotechnologies, Université Toulouse III, Toulouse, France, [3]Lebanese University- Faculty of Medecine, BEIRUT, Lebanon, [4]Lebanese University-Faculty of Pharmacy, Beirut, Lebanon

Background and aims: Stroke symptoms are common among people without history of stroke or transient ischemic attack (TIA). Stroke symptoms may represent stroke episodes that failed to reach the threshold for clinical diagnosis. The Middle East region is lacking data on the epidemiology of stroke. This study aimed to assess in the Lebanese population the prevalence of self-reported stroke symptoms in a stroke and TIA free population, and the association of these symptoms with major risk factors for stroke.

Methods: We carried out a cross-sectional study using a multistage cluster sample from all over Lebanon. We interviewed residents aged 40 years and more. Stroke symptoms were assessed using the Questionnaire for Verifying Stroke-Free Status.

Results: We included 1460 individuals (mean age 56.7 ± 12.4 years; 763, 52.3% women). 175 individuals (12.1%, 95% confidence interval [CI] 9.9%-14.3%) had experienced at least one stroke symptom. Arterial hypertension (odds ratio [OR] 4.36; 95% CI 2.68-7.11), regular physical activity (OR 0.43; 95%CI 0.25-0.74), current waterpipe smoking (OR 4.06; 95% CI 2.42-6.82), cumulative cigarettes' smoking >7 pack-years (OR 2.44; 95%CI 1.53-3.91), history of heart disease (OR 3.44; 95%CI 2.07-5.75), Mediterranean diet score (OR 0.87 95%CI 0.76-0.99) and the Beirut distress scale (BDS-22) (OR1.04; 95%CI 1.02-1.06) were found to be associated with stroke symptoms.

Conclusion: This is the first study conducted in Lebanon, assessing stroke symptoms among stroke-free residents. Our study showed that almost 1 of 8 residents without history of stroke or TIA has had stroke symptoms. Major vascular risk factors are associated with these symptoms leaving place for prevention strategies.

Disclosure: Nothing to disclose

P1270

Epidemiological data on the association of lacunar stroke and primary intracerebral hemorrhage: significant decline in incidence from 1998 to 2011

M.J.M.P. Correia[1], R. Magalhães[2], R.J.D.R. Felgueiras[1], M.C. Silva[2]

[1]Porto, Portugal, [2]Instituto Ciências Biomédicas Abel Salazar, Population Study Department, Porto, Portugal

Background and aims: Lacunar stroke and intracerebral haemorrhage share the hypertension as major risk factor. It would be expected that the chronic control of blood pressure would decrease incidence of both pathologies. In this study we aim to compare trends in incidence of lacunar stroke and primary intracerebral haemorrhage eleven years apart.

Methods: Two prospective population-based studies (1998-2000 and 2009-2011) were used to estimate changes in stroke incidence. Identical definitions and sources of information were used to ascertain all first-ever-in-a-lifetime strokes occurring in the metropolitan area of Porto. The Oxfordshire classification was used to define lacunar stroke. Patients were observed at onset and at three months.

Results: Between 1998 and 2011, ischemic stroke incidence decreased from 2.02 (95% CI, 1.81-2.24) to 1.61 (95% CI, 1.48-1.73) and primary intracerebral haemorrhage incidence decreased from 0.45 (95% CI, 0.36-0.57) to 0.23 (95% CI, 0.19-0.29). Among ischemic stroke subtypes, LACI decrement from 0.79 (95% CI, 0.66-0.92) to 0.43 (95% CI, 0.36-0.49) was the major contributor for the declining of ischemic stroke incidence. The decrement in LACI incidence was mostly evident in patients older than 65 and cerebral haemorrhages decreased along all age-groups.

Conclusion: The decrement of lacunar stroke incidence and of intracerebral haemorrhage incidence was similar and significant. Probably this trend results from preventive strategies for controlling blood pressure in the community. This epidemiological data corroborate hypertension as a major common underlying pathology for both entities.

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P1271

The Brunei epidemiological study in stroke and multiple scelrosis (BEST) - a door-to-door survey

U. Meyding-Lamadé[1], A. Lupat[2], E.M. Craemer[3], M. Luissin[2], R. Wagner[3], H. Becher[4]

[1]Krankenhaus Nordwest, Klinik für Neurologie, Frankfurt am Main, Germany, [2]Universiti Brunei Darussalam, Negara, Brunei Darussalam, [3]Krankenhaus Nordwest, Department of Neurology, Frankfurt am Main, Germany, [4]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Background and aims: Stroke, the 2nd common cause of death and the leading cause for permanent disability,it has enormous emotional and socioeconomic impact on patients. In 2011,WHO reported that 6.15 million people suffer from stroke worldwide. Aim is to investigate the distribution and determinants of stroke in the population. The information on prevalence of stroke is of utmost importance especially in the perspective in health policy making.

Methods: A cross-sectional study is performed among inhabitants of Brunei aged 18 years or older. Data are collected through door-to-door visits with the use of a standardized questionnaire. Blood pressure was measured twice during the interview. Participants targeted at intervals by means of the Poisson distribution to ensure representativeness of the population.

Results: We will only report preliminary findings. From October 2013 until March 2014, 2991 participants were interviewed. Mean age was 40.0±15.0 years. Hypertension, one of the major risk factors for stroke, has a high prevalence. The mean body mass index was 26.7±6.0kg/m^2, and the prevalence of obesity was found to be high with 24% overall.

Conclusion: Observations regarding hypertension and BMI, especially in the younger age groups were alarming. Comparing our study to studies from other countries, we find a significantly higher blood pressure in younger age groups. Public health policy makers should look into the planning and establishing of adequate resources for the diagnosis and the treatment of stroke and establish prevention programs to reduce risk factor prevalence.

Disclosure: Nothing to disclose

P1272

Familial, autosomal-dominant neurodegenerative parkinsonism with cognitive deterioration spanning five generations in a genetically isolated population of south-eastern Moravia, Czech Republic

L. Mikulicova[1], K. Mensikova[1], P. Kanovsky[1], M. Godava[2], P. Otruba[1], M. Kaiserova[1], M. Vastík[1], R. Vrtel[2], R. Vodicka[2], T. Bartonikova[1], S. Kurcova[1], P. Jugas[3], J. Ovecka[4], F. Dvorsky[5], L. Sachova[5]

[1]University Hospital Olomouc, Neurology, Olomouc, Czech Republic, [2]Univerzity Palacky, Departnent of Medical Genetics and Fetal Medicine, Olomouc, Czech Republic, [3]General Practicioner, Veselí nad Moravou, Czech Republic, [4]General Practicioner, Lipov, Czech Republic, [5]General Practitioner, Velká nad Veličkou, Czech Republic

Background and aims: An epidemiological study conducted over four years revealed an increased prevalence of neurodegenerative parkinsonism in a small, isolated region (10 villages, with a combined population of 8664, with approx. 2927 over 50 years of age) of south-eastern Moravia, Czech Republic. To obtain more detailed medical history information about the relatives of individuals with confirmed parkinsonism in an isolated region with a rural population in south-eastern Moravia, Czech Republic.

Methods: Detailed genealogical research was performed on the families of all the subjects with confirmed parkinsonism and the pedigrees were compiled; these were further amended on the basis of information obtained through a consecutive door-to-door survey and by means of local municipal and church registers.

Results: In the first stage, three large pedigrees with a familial occurrence of parkinsonism were found; two of them originated in one of the region's villages. In the second stage, these two pedigrees were completed into one large family tree.

Conclusion: The high prevalence of parkinsonism in the researched area is caused by the familial aggregation of parkinsonism that was found in two large family trees. This familial aggregation of parkinsonism is probably the result of the genetic isolation of the regional population due to the very low migration rate of its inhabitants to neighboring regions in the last two centuries.

Disclosure: Supported by the grants: IGA MZ CR NT – 14407 and IGA LF UP – 2014-018.

P1273

Does abnormal temperature and rapid changes of atmospheric pressure affect prevalence of stroke? Short-term effect of climate.

O. Mukalova

Minsk, Belarus

Background and aims: There is inconsistence of evidence in literature about sort term effects of climate factors on acute cerebrovascular diseases. Our aim was to investigate relationships between short-term climate factors, such as temperature and atmospheric pressure and stroke.

Methods: We obtained all records 1 Jan 2013 – 30 Sept 2014 from emergency healthcare registry of City of Minsk, Belarus, to estimate daily proportion of stroke. Only records with non-missing doctor-validated ICD10 codes were used to determine cases (ischemic, hemorrhagic or unspecified stroke). We applied linear time-series regression models for stationary data to assess relationships between stroke and rapid 48h changes of atmospheric pressure, daily average and maximum temperature, and abnormally high temperature.

Results: During the period, there were 993,812 records with daily average of 1,635 and 52 of total calls and stroke cases (3%), respectively. Mean age of sample was 47.3 years (SD27.7) with proportion of women 55%; of stroke subset – 67.4 years (SD 13.1) with 57% of women. Highest peaks of stroke was in April 4.3% and 5.1% in July; lowest – in December – 2.1%. Final model was adjusted for season, month, day of the week, non-weekend holidays, as well as main predictors. Proportion of stroke was 0.5% (95%CI -0.2-1.1) higher over long weekends, 1.2% (95%CI -1.0-3.2) higher over 48h abnormal changes of atmospheric pressure and 2.4% (95%CI -0.5-5.6) higher during extremely high temperature, however insignificantly.

Conclusion: Our results suggest tendency to positive association of stroke with some climate factors, especially with abnormally high temperature. These findings need further confirmation.

Disclosure: Nothing to disclose

P1274

Birth month effect in multiple sclerosis: Is it a risk factor? A populatıon based study

M. Oztekin[1], N. Öztekin[2], M. Yılmaz[3], S. Bilen[3], F. Ak[3]
[1]MOH Ankara Diskapi Teaching and Research Hospital, Neurology, Ankara, Turkey, [2]Ankara, Turkey, [3]ANH Traning and Research Hospital, Neurology, Ankara, Turkey

Background: Multiple sclerosis (MS) is a complex disorder, and the main causal factors seem to be environmental and enviromental -genetic interactions. In recent years, a month of birth effect on multiple sclerosis (MS) risk has been reported from different countries. The aim of the study is to determine whether risk of multiple sclerosis (MS) is associated with month of birth in a population based study, and if factors related to month of birth interact with genetic risk.

Methods: The study is designed as population based and family based controls and familial cases are also analysed. A post hoc pooled analysis of 1291 patients with definite MS, all born in this region were included in the study from the MS databases of two major centres for MS in Ankara. The birth dates of patients were recorded and grouped according to the month of birth. The patients were also recorded about their demographic features.

Results: The results of our study revealed that significantly fewer patients with MS were born in November compared with controls from the population and unaffected siblings. A pooled analysis showed that significantly more people with MS were born in April and May.

Conclusion: The results of our study, are in accordance with previous studies, have shown that there is a relationship between month of birh an MS accumulation. The latitude of Ankara may be an explanation for the time span (April-May) in our results.The results of our our data showed that there is an association between the month of birth and MS.

Disclosure: Nothing to disclose

Neuroimaging 1

P1275

Consistent decreased functional connectivity among the main cortical and subcortical functional networks in MS: relationship with disability and cognitive impairment

M.A. Rocca[1], P. Valsasina[2], L. Vacchi[1], V.M. Leavitt[3], G. Comi[4], A. Falini[5], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, [1]Neuroimaging Research Unit, Milan, Italy, [3]Columbia University Medical Center, Department of Neurology, New York, USA, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [5]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To explore resting state (RS) functional connectivity (FC) abnormalities within the main cortical/subcortical brain networks in a large cohort of patients with multiple sclerosis (MS) with different clinical phenotypes.

Methods: RS fMRI and a complete neuropsychological evaluation were obtained from 202 MS patients (118 relapsing-remitting [RR], 43 secondary progressive [SP], 28 benign and 13 primary progressive MS) and 98 healthy controls. RS FC analysis was done using a seed-voxel correlation with seven major cortical/subcortical hubs (posterior cingulum, inferior parietal cortex, cuneus, postcentral gyrus, cerebellum, thalamus, and amygdala). Between-group differences of RS FC and correlations with clinical/neuropsychological scores were evaluated (SPM8).

Results: Compared to controls, MS patients showed a widespread reduction of RS FC in all cortical/subcortical networks. In the visual and somatosensory networks, RS FC decrease was mainly found in bilateral parietal and superior occipital regions. RS FC decrease within the default and dorsal attention network involved the bilateral precuneus and superior/middle frontal regions. Decreased cerebellar RS FC was observed in the dorsal attention, thalamic and cerebellar networks. A decreased RS FC between the thalamus and frontal regions was also detected. Compared to RRMS, SPMS patients showed reduced RS FC in the somatosensory and thalamic networks. Decreased cerebellar RS FC was correlated with higher EDSS. Decreased RS FC in frontal regions of the dorsal attention and default networks correlated with worse cognitive performances.

Conclusion: Cortical/subcortical RS FC is consistently reduced in MS patients and is clinically relevant, since it correlates with disability and cognitive impairment.

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P1276

Ultrasound fusion imaging for intracranial haemorrhage – a transcranial duplex ultrasound study

S. Schreiber[1], J.M. Valdueza[2], G. Bohner[3], F. Connolly[1]

[1]Charité Universitätsmedizin Berlin, Dept. of Neurology, Berlin, Germany, [2]Segeberger Kliniken, Dept. of Neurology, Bad Segeberg, Germany, [3]Charité Universitätsmedizin Berlin, Dept. of Neuroradiology, Berlin, Germany

Background and aims: Transcranial duplex sonography (TCS) can identify acute intracranial hemorrhage as hyperechogenic B-mode lesions. However, the sensitivity is low as a high percentage of lesions cannot be found, even if the location is known from CT or MRI. Ultrasound fusion imaging (UFI) is a new technique which allows TCS analysis in freely selectable insonation planes with simultaneous visualisation of corresponding pre-registered CT or MR images. We report about its application in a pilot series of patients with acute intracranial hemorrhage.

Methods: Patients were recruited from our stroke- or intensive care unit if routine CT diagnosed acute intracranial hemorrhage. UFI was performed as an acute combined image sequence of TCS and the routine CT aiming to depict the hemorrhage by insonating exactly within the image plane of the hemorrhage using an Esaote Mylab Twice ultrasound system (Italien, Padua) with the commercially available software "Virtual Navigator". Serial follow-up investigations were performed in all patients with positive ultrasound findings.

Results: 25 patients were studied including 21 mass hemorrhages (1 cerebellar, 9 cortical, 11 basal ganglia), 3 cavernoma hemorrhages (1 cortical, 2 basal ganglia) and 1 subdural hematoma. Application of the UFI technology was possible in all studied patients. Hemorrhage was identified on TCS sequences as marked or moderate hyperechogenicity in a high percentage of mass hemorrhages, reproducible on subsequent serial UFI investigations. Only one out of three studied cavernoma hemorrhages could be visualised.

Conclusion: UFI is a promising technique, which should be further evaluated concerning its applicability and reliability in the diagnostic follow-up of intracranial hemorrhage.

Disclosure: S. Schreiber has been supported by Esaote by lending of a research Mylab Twice/Virtual navigator ultrasound system.

P1277

Ultrasound MRI fusion imaging in muscle disease

K. Irlbacher[1], F. Connolly[1], H. Engelhardt[1], W. Stenzel[2], K. Hahn[1], S. Schreiber[1]
[1]Charité Universitätsmedizin Berlin, Dept. of Neurology, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Dept. of Neuropathology, Berlin, Germany

Background and aims: MRI and ultrasound are helpful tools in the diagnostic workup of muscle diseases. MRI is the best technique to identify muscle involvement patterns to find the optimal location of a muscle biopsy. However, MRI can not be taken into the operating room. US-MRI-fusion imaging (UFI) is a new bedside technique permitting a combination of live ultrasound with simultaneous visualisation of exactly matched MR images, derived from pre-registered datasets. We report UFI application in a series of patients with muscle diseases, scheduled for biopsy.

Methods: Patients were recruited from our hospital if routine pre-biopsy MR-imaging (spin echo T1-, T2, STIR) was available. UFI was performed as an additional image sequence during pre-biopsy ultrasound using an Esaote Mylab Twice system (Italy, Padua) equipped with the "Virtual Navigator" software.

Results: UFI was performed in 57 patients. (muscle of the: upper leg 37, lower leg 14, hip 2, upper arm 4, lower arm 1). MRI-defined muscle segments of interest could be identified in all patients with the need of minor matching corrections during the insonation process. Ultrasound-MR comparison of affected muscles were not aleways congruent. E.g. in regions with MR-suspected edema, US demonstrated tissue hyperechogenicity, suggestive of fibrosis.

Conclusion: UFI is a promising technique, which should be further evaluated concerning its applicability and reliability in the diagnostic of muscle diseases. Comparison of MRI and US might help to further differentiate muscle tissue alterations. However, this hypothesis has yet to be confirmed e.g. by histological evaluations.

Disclosure: S. Schreiber has been supported by Esaote by lending of a research Mylab Twice/Virtual navigator ultrasound system.

P1278

Exploration of functional and structural cerebral modifications underlying executive functioning impairment after an acute coronary syndrome: a multimodal MRI study.

C. Bernard[1], G. Catheline[2], T. Couffinhal[3], S. Lassalle-Lagadec[2], D. Callaert[1], M. Allard[2], I. Sibon[4]
[1]Univ. Bordeaux, INCIA, UMR 5287, Bordeaux, France, [2]Univ. Bordeaux, INCIA, UMR 5287, EPHE, Bordeaux, France, [3]Centre Hospitalier de Bordeaux, Centre d'Exploration, de Prévention et de Traitement de l'Athérosclérose - Echographie vasculaire (CEPTA), Bordeaux, France, [4]CHU Pellegrin, Bordeaux, France

Background and aims: Three to 6 months after an acute coronary syndrome (ACS), cognitive impairments are observed in more than 30% of the patients, mainly in executive functioning. The aim of this study was to investigate the cerebral anatomo-functional substratum of this executive dysfunction using multimodal MRI.

Methods: 33 patients were recruited 4±1 months after an ACS. Executive functions were evaluated with the Trail Making Test B (TMTB) at baseline and 6 months later. We used normative data to determine the cognitive status of the patients at baseline and follow-up. The integrity of the whole cerebral macrostructure and microstructure was explored using Voxel-Based Morphometry and Tract-Based Spatial Statistics, respectively. Whole-brain resting state functional connectivity was investigated using Network-Based Statistics.

Results: We identified 15 'cognitively normal' patients, 10 'transient impaired' patients with an impairment only at baseline and 8 'impairing' patients with an impairment only at follow-up. After a first ACS, no structural difference was observed between impaired and cognitively normal patients. At the functional level, compared to the 'cognitively normal' group, the 'transient impaired' patients presented an increased functional connectivity in a network centered on middle orbito-frontal regions, whereas the 'impairing' patients presented only a trend to a decreased of functional connectivity.

Conclusion: Two types of patients could be identified: those with a transient impairment associated with a hyper-connected brain network and those with a delayed impairment with a trend to a decreased connectivity. Both would need further attention because they could have an increased risk, with different time trends, to develop permanent cognitive disorder.

Disclosure: Nothing to disclose

P1279

Diagnostic and prognostic validity of quantitative EEG and SPECT markers in the early diagnosis of cognitive diseases

W. Staffen[1], Y. Höller[1], H. Zauner[2], E. Trinka[1], N. Strobl[3]
[1]Paracelsus Medizinische Privatuniversität , Neurology, Salzburg, Austria, [2]Rehabilitationszentrum Großgmain, Grossgmain, Austria, [3]Paracelsus Medizinische Privatuniversität, Neurology, Salzburg, Austria

Introduction: Dementia is a devastating disease with increasing numbers worldwide and an early diagnosis would provide fast and effective care. Single photon emission computed tomography (SPECT) and Quantitative Electroencephalography (qEEG) have become powerful tools in routine diagnostics. We investigated, whether both individual and combined use of such tools can discriminate between patients with Alzheimer's disease (AD), amnestic Mild Cognitive Impairment (aMCI) and Subjective Cognitive Complaints (SCC) and between patients with progressive (PaMCI) vs. stable aMCI (SaMCI).

Methods: 160 patients (36 AD, 56 aMCI, 68 SCC) from the Memory Clinic Salzburg were retrospectively rediagnosed and grouped according to follow-up in PaMCi and SaMCi. Relative cerebral blood flow of 16 anatomical regions was assessed in SPECT and quantitative parameters were extracted for qEEG (Hjorth complexity, mobility, activity; brainrate; Hurst Exponent). Correlations between cerebral hypoperfusion in SPECT and dysfunction in qEEG were sought.

Results: Differentiation of AD vs. SCC and AD vs. aMCI was significant in every SPECT region. No significant difference between aMCI and SCC was found. qEEG showed significant discrimination between AD vs. SCC and aMCI vs. SCC. Combining SPECT and qEEG showed increased accuracy for AD vs. aMCI. PaMCI vs. SaMCI differed significantly in left temporal areas (SPECT) and right parietal-occipital regions (qEEG).

Conclusion: qEEG dysfunctions occur at SCC stage whereas neurodegenerative hypoperfusion is seen in later stages. Thus a combination of qEEG and SPECT could enable to predict the progression of cognitive decline when aMCI stage has been reached. Further research is needed.

Disclosure: Nothing to disclose

P1280

Brain atrophy rates and sustained disability over 10 years in multiple sclerosis

M.L. Stromillo[1], A. Giorgio[1], M. Battaglini[1], F. Rossi[1], A. De Leucio[1], M.L. Bartolozzi[2], M. Baldini[2], L. Guidi[2], M.P. Sormani[3], E. Portaccio[4], M.P. Amato[4], N. De Stefano[1]
[1]University of Siena, Sienna, Italy, [2]Hospital of Empoli, Empoli, Italy, [3]University of Genoa, Biostatistics Unit, Department of Health Sciences, Genoa, Italy, [4]University of Florence, Florence, Italy

Background and aims: Brain atrophy is considered a significant marker of disease progression in multiple sclerosis (MS). We assessed 10-year brain atrophy rates in MS patients and normal controls (NC).

Methods: At baseline, we studied 110 MS patients (relapsing-remitting [n=94], secondary progressive [n=8], primary progressive [n=8]) and NC (n=16). The two study groups were assessed again after 10.3±0.6 years. We acquired conventional brain MRI at both time-points with the same protocol. Percent volume change in the whole brain (PBVC), grey matter (PGMVC) and white matter (PWMVC) were computed using modified SIENA/SIENAx software.

Results: MS patients had greater PBVC/y (-0.5±0.22% vs.-0.3±0.12%, p=0.003), PGMVC/y (-1.01±0.46% vs -0.73±0.19%, p=0.03) and PWMVC/y (-0.18±0.27% vs -0.01±-0.13%, p=0.03) than NC. In worsening patients (EDSS change≥1), PBVC/y was greater than in clinically stable patients (EDSS change<1) (p=0.007). In patients with minimal/no disability at baseline (EDSS≤3), PBVC/y and PGMVC/y were faster in patients who became disabled over the 10-year follow up (EDSS>3) than in those who did not (p<0.02). In a multivariate analysis, EDSS change >2 after 10 years was best correlated with the combination of PGMVC/y, baseline T1-lesion count and annualized relapse rate≥0.5 (accuracy=82%, p<0.001).

Conclusion: Brain atrophy over 10 years is almost twice as faster in MS patients than in NC and occurs in both GM and WM. In the long term, sustained clinical worsening is best associated with progression of GM atrophy, alongside destructive lesions at baseline and high relapse rate. This is particularly true in patients with low disability at baseline.

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P1281

Dopamine transporter SPECT provides instrumental diagnosis of akinetic crisis of parkinsonism and of neuroleptic malignant syndrome

A. Thomas[1], G. Martino[2], M. Capasso[3], M. Nasuti[4], L. Bonanni[1], M. Onofrj[1]

[1]University Chieti Pescara, Dept of Neurosciences, Imaging and Medical sciences, [2]Ospedale Clinicizzato Chieti, Dept of Radiology, [3]ospedale clinicizzato Chieti, Dept of Neuroscience, imaging and Medical sciences, Chieti, Italy, [4]ospedale clinicizzato Chieti, Dept. of Radiology, Chieti, Italy

Proposal: Akinetic Crisis (AC) is akin to Neuroleptic Malignant Syndrome (NMS) and is the most severe and possibly lethal complication of parkinsonism. Diagnosis is today based only on clinical assessments yet is often marred by concomitant precipitating factors. Our purpose is to evidence that AC and NMS can be reliably evidenced by FP/CIT Single Photon Emission Computerized Tomography (SPECT) performed during the crisis.

Methods and Materials: Of 6 patients with AC with severe akinesia, 5 were affected by Parkinson's Disease or Lewy body dementia and the crisis was categorized as AC. 1 was diagnosed as NMS because of exposure to risperidone. In all FP/CIT SPECT was performed in the acute phase. SPECT was repeated 3-6 months after the acute event in 5 patients. Semi quantitative evaluations were used to assess binding potentials (BP). As all patients were treated with life supporting measures and 4 patients were treated with apomorphine, at the same doses as used in the emergency treatment.

Results: During AC or NMS, BP values in caudate and putamen were reduced by 95-80% to noise level of the 97% inferior confidence limit, with a nearly complete loss of striatum dopamine transporter binding similar to the „ burst striatum". However the follow-up re-evaluation in surviving patients showed a recovery of values by 250-650% to the range expected of parkinsonism at the same disease duration. No binding effects of apomorphine were observed.

Conclusion: By showing the outstanding binding reduction, presynaptic dopamine transporter ligand can provide instrumental evidence of AC in Parkinsonism and NMS.

Disclosure: Nothing to disclose

P1282

Clinical, neuropsychological and MRI findings in a cohort of Friedreich's Ataxia patients

M. Vavla[1], F. Arrigoni[2], E. Petacchi[3], A. Nordio[4], A. de Luca[2], E. Russo[3], S. Pizzighello[3], G. d'Angelo[5], D. Facchin[3], M.T. Armellin[3], G. Paparella[3], E. Carraro[3], A. Martinuzzi[3]

[1]Conegliano, Italy, [2]IRCCS E.Medea Research Institute, Neuroimaging Unit, Bosisio Parini, [3]Scientific Institute IRCCS E. Medea, Conegliano and Pieve di Soligo Research Centre, Conegliano, Italy, [4]IRCCS E.Medea Research Institute, Neuroimaging Unit, Bosisio, Italy, [5]IRCCS E.Medea Research Institute, Functional Neurorehabilitation Unit for Neuromuscular Disorders, Bosisio Parini, Italy

Background and aims: Friedreich's ataxia (FRDA) is an autosomal-recessive neurodegenrative conditions caused by a GAA repeat triplet. There are no quantitative objective biomarkers to show reliable correlations with progression rate and disease severity.

Methods: 21 early-onset molecularly-defined FRDA patients underwent clinical-neuropsychological assessment. A subgroup of patients (n=17) and age-matched healthy controls (HC) underwent a neuroimaging study protocol on a 3T-MRI (DTI, fMRI). Non-parametric voxel-based permutations were performed on the WM-maps regions-of-interest (ROI), via a general linear model (GLM) ($p<0.05$). An fMRI sequence was acquired during a simple block-design finger-tapping task.

Results: All patients were homozygous for GAA expansion (mean GAA1 653.7±221), but one with a point-mutaion/170GAA. Age-at-onset: 10.6±4.6yrs, age-at-assessment 26.9±10.3yrs, disease-duration 16.3±8.8yrs. Disease-severity: SARA 21.4±7.8; ICARS 53±18.6; FARS-neur.exam 62.7±18.4. The motor performance influenced the IQtot. Deficit on executive and attentive functions were observed. We found altered FA and MD parameters, through voxel- and ROI-based analysis, in the cerebellar peduncles; corticospinal, lemnisceal systems, major commissural fibres, thalamic and optic radiations. A finger-tapping task demonstrated significantly higher cerebellar-cortex activation (lobule V, IV) in HC compared to FRDA.

Conclusion: We report our clinical and neuroimaging experience of a FRDA cohort in order to explore WM connectivity and motor dysfunction. DTI changes in selected areas and BOLD-signal in the cerebellar, ipsilateral cerebellar-cortex in response to a simple motor task show strong intergroup-discriminating power and may prove to be useful paraclinical disease markers. A longitudinal study is needed to investigate and validate the sensitivity of these indicators.

Disclosure: Nothing to disclose

P1283

Susceptibility weighted MRI can help differentiating pathogenesis of white matter lesions in MS and CNS inflammatory vasculopathies

L. Vuolo[1], G. Emmi[2], G. Carlucci[3], A.M. Repice[3], C. Mechi[3], M. Grammatico[1], D. Prisco[2], E. Silvestri[4], A. Barilaro[1], L. Emmi[5], L. Massacesi[3]

[1]Careggi Hospital, Department of Neuroscience, Florence, Italy, [2]Careggi Hospital, Departement of experimetal and clinic medicine, Florence, Italy, [3]Careggi University Hospital-University of Florence, Neurology [2], Florence, Italy, [4]Careggi HospitalUniveristy of Florence, Departement of experimetal and clinic medicine, Florence, Italy, [5]Careggi Hospital, Interdisciplinary internal Medicine-Autoimmune Diseases, Florence, Italy

Background and aims: MRI is a sensitive tool for detecting brain white matter (WM) lesions, but its specificity may be low, particularly for lesions associated to chronic inflammatory vasculopathies, often difficult to differentiate from multiple sclerosis (MS) lesions. However in the WM, MS lesions develop along a vein, a feature that could help characterize differences. In this study the frequency of perivenular lesions (PVL) was used as a marker for differentiating WM MS lesions from those observed in systemic autoimmune diseases with inflammatory vasculopathies (SAD) and brain involvement.

Methods: Patients with MS (n= 30) and SAD involving brain (n= 20), have been selected for MRI (1.5T) evaluation. Susceptibility weighted images (SWI) two minutes after gadolinium injection and volumetric FLAIR sequences were acquired. The total number of lesions was analyzed in the FLAIR scans, whereas the venules and their relations with the lesions, in the SWI scans co-registered on the FLAIR scans. Lesions were considered perivenular, if the lesional hyperintensities completely surrounded a vein in at least 1 plane. A vein was defined as a morphologically compatible hypointense signal visible in at least 2 perpendicular plans.

Results: Preliminary data were obtained in 424 lesions (n=10 MS, 3 SAD). Number of lesions was lower in MS, whereas their volume was larger. Mean percentage of PVL was significantly higher ($p<0.05$; Wilcoxon's test) in MS patients (81%±11) than in SAD (9.4%±10).

Conclusion: Although PVL can be detected also in SAD, their proportion out of total lesions seems remarkably higher in MS, suggesting they represent a useful marker of disease

Disclosure: Nothing to disclose

Sleep disorders 1

P1284

Quality of sleep in patients receiving androgen deprivation therapy for prostate cancer: evaluation of sleep disturbance, depression and fatigue

A. Koskdereliogluˡ, M. Gedizlioglu[1], Y. Ceylan[2], B. Gunlusoy[2], N. Kahyaoglu[1]
[1]Izmir Bozyaka Education and Research Hospital, Department of Neurology, Izmir, Turkey, [2]Izmir Bozyaka Education and Research Hospital, Department of Urology, Izmir, Turkey

Background and aims: Androgen deprivation is a therapeutic option for patients with prostate cancer. However, it has negative effects on sleep quality and psychological condition. Here, we evaluated the appearance of sleep disturbances in patients on androgen deprivation therapy (ADT).

Methods: Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS) were administered to consecutive prostate cancer patients who underwent radical prostatectomy and are presently either under adjuvant ADT or followed in an unmedicated program (non-ADT). The results in ADT and non-ADT groups in addition to the demographic data and the features of the malignancy were statistically compared.

Results: Of the 67 patients enrolled, 31 (46.3%) were receiving adjuvant ADT and 36 were not. Age, disease duration and education level showed no difference between the two groups. Compared with non-ADT group, the patients receiving ADT showed higher levels of depression (p=0.003), worse quality of sleep (p=0.001) and severe fatigue(p=0.005). ADT was significantly associated with depression, fatigue, and poor sleep. There was no significant difference between the ADT and non-ADT patients in terms of excessive daytime sleepiness measured with ESS(p=0.249). PSQI scores showed a mild correlation with age and disease duration (p=0.048, p=0.05, respectively). However, a high correlation with oncologic stage of the tumor, BDI, and FSS scores was observed (p=0.027, p=0.0001, p=0.0001, respectively).

Conclusion: Adjuvant ADT is associated with worse sleep quality, depression and fatigue in patients with prostate cancer. To recognize such symptoms may remarkably improve their quality of life.

Disclosure: Nothing to disclose

P1285

The polymorphisms of ABCB1 gene influence the therapeutic efficacy of modafinil and venlafaxine in narcoleptic type 1

M. Moresco[1], L.N. Riccardi[2], F. Pizza[3], L. Caporali[4], S. Pelotti[2], G. Plazzi[3], V. Donadio[1]
[1]university of Bologna, Biomedical and Neuromotor Sciences (DIBINEM), Bologna, Italy, [2]university of Bologna, Medical and Surgical Sciences (DIMES), Bologna, Italy, [3]university of Bologna, Biomedical and Neuromotor Sciences (DIBINEM); IRCCS Istituto delle Scienze Neurologiche, Bologna, Bologna, Italy, [4]university of Bologna, IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy

Background and aims: Narcolepsy type 1 (NT1) is a chronic hypersomnia characterized by daytime sleepiness and cataplexy. NT1 treatments mostly target individual symptoms: wake-promoting agents (e.g. modafinil) are effective on sleepiness, antidepressants (e.g. venlafaxine) on cataplexy, while sodium oxybate (SO) is the only drug effective on both. NT1 patients variably respond to modafinil and venlafaxine thus affecting compliance. Given the potential influence of drug transmembrane transport (glycoprotein-P) and/or metabolism (by cytochrome P450) on clinical response, we addressed the relation between genetic polymorphisms in ABCB1 or CYP450 genes and clinical response to modafinil and venlafaxine in NT1 patients.

Methods: Individual drug response and genotypes were assessed in 107 NT1 patients (males/females 64/43, mean age 38 years, SD±21.011) treated with modafinil and/or venlafaxine at stable doses for at least three months. Minisequencing was performed to detect single nucleotide polymorphisms (SNPs) in ABCB1 and in CYP450 genes (CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5). Patients with different responses to treatment were contrasted.

Results: ABCB1 polymorphisms were significantly associated with clinical response. The wild-type genotype 1236C>T (P=0.011) and 2677C>T/A (P=0.023) were more represented in the modafinil non-responder versus responder group. Consequently, the haplotype 1236T/2677T/3435T was more represented (P=0.006) in the modafinil responder versus non-responder group. Similarly, the wild-type genotype of 1236C>T was more frequent (P=0.022) in the venlafaxine non-responder versus responder patients. Finally, CYP450 genes did not show any significant association with treatment response.

Conclusion: ABCB1 genetic variants modulate therapeutic response to modafinil and venlafaxine and may partly explain pharmacoresistance in NT1 patients.

Disclosure: Nothing to disclose

P1286

Insomnia and mental disorders: data from primary care

J. Peceliuniene[1], A. Bunevicius[2], V. Kasiulevicius[1], N. Mickuviene[3]
[1]*Vilnius University, Clinic of Internal Medicine, Family practice and Oncology, Vilnius, Lithuania,* [2]*Institute of Neurosciences of the LUHS, Laboratory of Clinical Research, Kaunas, Lithuania,* [3]*Behavioral Medicine Institute, LUHS, Palanga, Lithuania*

Background and aims: Mental disorders (MD) are highly prevalent but poorly recognized in primary care (PC). Insomnia is most often thought of as both a medical sign and a symptom that can accompany several psychiatric disorders. The aim of the study was to evaluate the rate and recognition of mental disorders in PC.

Methods or Materials or Case Report: 998 consecutive PC adult patients (average age 50,16±18,75), 320 male and 678 female, were evaluated for MD twice: first time by general practitioner (GP), using his or her routine method, and, secondly, by using MINI International Neuropsychiatric Interview (MINI).

Results: Only 44.8 % of PC patients, who had no psychiatric diagnosis after GP evaluation, had no mental disorders detected by MINI (Table1). MD were diagnosed for minority of patients (150 patients: 38 (11.9 %) male, 112 (16.5%) female) by general practitioner, and the most common (30 %) diagnosis was insomnia, diagnosed in 50 patients of the sample.

Table 1 *Current psychiatric diagnoses established by MINI as function of psychiatric diagnoses documented by primary care physician*

	Current psychiatric diagnoses established by MINI			
	Major depressive episode n (%) N=152 (100.0)	Any anxiety disorder n (%) N=212 (100.0)	Alcohol abuse n (%) N=348 (100.0)	Suicidal ideation n (%) N=61 (100.0)
Documented psychiatric diagnosis				
No diagnosis (n=848)	110 (72.3)	179 (84.4)	313 (89.9)	45 (73.7)
Depression (n=45)	16 (10.5)	32 (15.0)	8 (2.2)	7 (15.6)
Anxiety disorder (n=30)	6 (3.9)	15 (7.0)	9 (34.8)	3 (4.9)
Insomnia (n=50)	11 (7.2)	20 (9.4)	10 (20)	4 (6.5)
Other (n=25)	9 (5.9)	16 (7.5)	8 (2.3)	2 (3.2)

The split between mental diagnoses by general practitioner and MINI International Neuropsychiatric Interview

Conclusion: Mental disorders are highly prevalent, however, poorly recognized in primary care. Our findings suggest that the use of standard screening tool for mental disorders such as MINI could play a critical role in diagnosing psychiatric disorders in primary care.

Disclosure: Nothing to disclose

P1287

Nocturnal sleep stage transitions identify narcolepsy type-1 among central disorders of hypersomnolence

F. Pizza[1], S. Vandi[1], M. Iloti[1], C. Franceschini[2], R. Liguori[1], E. Mignot[3], G. Plazzi[1], V. Donadio[1]
[1]*University of Bologna, Bologna, Italy,* [2]*University of Parma, Parma, Italy,* [3]*Stanford University, Stanford, USA*

Background and aims: Previous studies disclosed high sleep-wake transitions in narcolepsy. We thus aimed at evaluating the reliability of nocturnal sleep dynamics in the differential diagnosis of central disorders of hypersomnolence.

Methods: 175 patients with hypocretin-deficient narcolepsy type 1 (NT1, n=79), narcolepsy type 2 (NT2, n=22), idiopathic hypersomnia (IH, n=22), and "subjective" hypersomnolence (sHS, n=52) undergoing polysomnographic (PSG) work-up including 48 hours of continuous PSG recording.

From nocturnal PSG conventional sleep macrostructure, occurrence of sleep onset REM period (SOREMP), sleep stages distribution and sleep stage transitions were calculated. Patient groups were compared, and receiver operating characteristic (ROC) curve analysis was used to test the diagnostic utility of nocturnal PSG data to identify NT1.

Results: Sleep macrostructure was mostly stable in the two nights of each diagnostic group. Narcoleptic patients had lower latency to REM sleep, and NT1 patients showed most awakenings, sleep stage transitions, and time spent in N1, as well as most SOREMPs at daytime PSG and at MSLT than all other groups. ROC curve analysis showed that nocturnal SOREMP (area under the curve of 0.724), percent of total sleep time spent in N1 (0.896±0.023), and the Wakefulness-Sleep transition index (0.796±0.034) had a good sensitivity and specificity profile to identify NT1, especially when used in combination (0.903±0.023), comparably to SOREMP number at continuous daytime PSG (0.899±0.026) and at MSLT (0.956±0.015).

Conclusion: Sleep macrostructure including stage transitions can identify NT1 among central disorders of hypersomnolence.

Disclosure: Nothing to disclose

P1288

Clinical trial design and strategies for developing pharmacological treatments for sleep bruxism

T. Roesel
Uniformed Services University of the Health Sciences, Department of Medicine, Bethesda, Maryland, USA

Background and aims: Sleep bruxism is a neurological movement disorder leading to fatigue, teeth attrition, temporomandibular joint pain disorders, and headaches. A recent Cochrane review identifies the need for randomized clinical controlled trials (RCTs) to better develop pharmacological treatments for bruxism. Therefore, a trial design for drug testing is proposed using a newly available device for bruxism assessment. To determine nocturnal bruxism events, this noninvasive portable device measures masseter activity and monitors heart rate. Sample sizes for RCTs are calculated based on the number of episodes of bruxism per night (E/N).

Methods: Data from Deregibus, et al. (Clinical Oral Investigations, 2014), was applied to the t-test for two independent variables from PS software with the following parameters: type I error probability of 0.05, power of 0.9, allocation of 1:1, and 50% decrease in the mean of 30.5 E/N, with a standard of deviation of 11.66 E/N.

Results: If the difference in the experimental and control means is 15 E/N (50% decrease), calculations reveal that 14 experimental and 14 control subjects are needed to reject the null hypothesis.

Conclusion: Assuming that a 50% reduction in E/N represents bruxism improvement, RCTs with this device are feasible, since only 28 study subjects are needed per trial. Though clonidine or clonazepam may reduce bruxism, the Cochrane review concluded that all studies so far have been inadequate. Thus, head-to-head drug trials and those using glutamate antagonists or γ-aminobutyric acid (GABA) active agents are proposed. Future studies are needed to identify pharmacological treatments that better control sleep bruxism.

Disclosure: Nothing to disclose

P1289

Restless legs syndrome and transdermal fentanyle: a case of augmentation

H. Santos-Canelles
Coaña, Spain

Background and aims: Augmentation consists of the exacerbation of restless legs syndrome (RLS) after the beginning of a therapy. It is a well known complication in patients treated with first line therapies like dopaminergic agonists, but not in other cases.

Methods: Retrospective study of a case of RLS associated to transdermal fentanyl treatment. Assessment includes past medical history, interview about RLS symptoms, blood tests, cranial CT and spinal MRI.

Results: A 70-year-old man starts treatment with 50mg TID because of a lumbar vertebral compression fracture. It is later changed into transdermal fentanyl (8.4mg/3 days) because of lack of efficacy. One year later, he starts having sporadically pain in his arms at nights that is relieved by movement. During the next two years symptoms become dayly and extend to his four limbs, worsening at nights though pain is present nearly all day. Ferritin levels and cranial CT are normal and spinal MRI shows a lumbar compression fracture. Pain disappears completely when rotigotine is started.

Conclusion: This is an atypical case of RLS both because of symptoms and also because of the drug associated to augmentation. Upper extremity symptoms only rarely develop into RLS. Besides, opioids such as tramadol and oxycodone are being used as a second-line treatment for RLS and augmentation has only been described in few patients treated with tramadol. In this case, transdermal fentanyl is associated to the beginning and worsening of RLS. Augmentation maybe shoud be considered as a possible complication in long term treatment of RLS with opioids.

Disclosure: Nothing to disclose

P1290

Obstructive sleep apnea syndrome in muscular versus neuronal disorders in children with Duchenne muscular dystrophy and spinal muscular atrophy

B. Zeydan[1], G. Incesu[2], G. Benbir[1], A. Aydin[3], S. Saltik[3], C. Yalcinkaya[1], D. Karadeniz[1]

[1]Istanbul University Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey, [2]Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey, [3]Istanbul University Cerrahpasa School of Medicine, Department of Pediatrics, Istanbul, Turkey

Background and aims: Obstructive sleep apnea syndrome (OSAS) is rare in children, but there is an increased risk in case of association with neuromuscular diseases. Aim of this study is to compare sleep architecture and presence of sleep-related breathing disorders in muscular versus neuronal disorders in children with Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).

Methods: We prospectively investigated children with DMD or SMA who were admitted to Child Neurology Clinics in Pediatrics/Neurology Departments for the last one year. Nine male children, whose parents agreed to participate, had polysomnography.

Results: Five children had DMD and 4 children had SMA. Mean ages were 9.6±2.6 and 5.2±4.6 (p=0.190), body mass index values were 18.2±8.9 and 16.2±2.6 (p=1.000) in children with DMD and SMA, respectively. Polysomnographic parameters (total sleep time, sleep latency, efficiency, percentages of sleep stages) were all similar. Apnea-hypopnea index (AHI) was normal (below 1/hour) in all DMD cases, whereas all children with SMA had OSAS with mean AHI of 6.7±3.5 per hour (p=0.016). Periodic leg movements in sleep(PLMS) were present in 40% of children with DMD, 75% of children with SMA. PLMS index was also higher in children with SMA (10.5±8.8 versus 3.0±4.2 per hour, p=0.159).

Conclusion: We interestingly observed that none of the children with DMD had OSAS, while all children with SMA had. Although these results should be confirmed in larger series, a very high comorbidity of OSAS in children with SMA is noteworthy and requires further attention to improve quality of life and respiratory status.

Disclosure: Nothing to disclose

P1291

The relationship between serum melatonin levels and seep evaluation scales in idiopathic Parkinson's disease

A. Uysal, B.I. Tiftikcioglu, Y. Zorlu

İzmir Tepecik Education and Research hospital, Neurology, Izmir, Turkey

Background and aims: Sleep disorders, seen during the entire course of the disease, is one of the non-motor complications of Idiopathic Parkinson Disease (IPD). Various sleep disturbances might be related to either disease symptoms, adverse effects of medications, or alterations in melatonin and other various sleep hormone levels. We aimed to compare patients diagnosed with IPD whom do not have sleep complaint with healthy controls by sleep evaluation scales, and serum melatonin levels.

Methods: 40 IPD patients (F/M:19/21) who are above 50 years of age and 40 healthy, age and sex-matched control subjects (F/M:20/20) without any neurological, endocrinological or sleep disorders were included in the study. Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were performed and serum melatonin levels were measured in blood samples taken at 00:00 and 05:00h in all subjects.

Results: There was a statistically significant difference between the two groups in terms of PSQI and ESS. Although the serum melatonin levels at two different time points during night time were lower in patients with IPD compared to healthy controls, these differences did not reach statistical significance. There was a significant but weak correlation between ESS scores and decrease in serum melatonin levels taken at 05:00 AM , but not between serum melatonin levels at 00:00 PM.

Conclusion: Although the sleep evaluation questionnaires such as Pittsburg Sleep Quality Index and Epworth Sleepiness Scale provide highly sensitive information on sleep disorders, the serum melatonin levels do not.

Comparison of Sleep Scale and Melatonin Levels

Sleep Scale	Patients (n=40)				Control (n=40)			
	Melatonin level 00:00		Melatonin level 05:00		Melatonin level 00:00		Melatonin level 05:00	
	r	p	r	p	r	p	r	p
Pittsburg Sleep Quality Index	-0.087	0.592	-0.099	0.544	-0.026	0.873	-0.157	0.335
Epworth Sleepiness Scale	-0.127	0.435	-0.353	0.025	-0.056	0.730	-0.076	0.641

Properties of patients with IPD

	Woman (n=19)	Man (n=21)	Total (n=40)
Age (year) (mean±SD)	66.21±8.34	70.24±7.18	68.32±7.92
UPDRS Score (mean±SD)	34.79±18.74	31.57±16.73	33.10±17.56
Hoehn-Yahr Score (mean±SD)	2.26±1.17	2.02±1.01	2.14±1.08
Period of disease (year) (mean±SD)	9.21±6.70	7.33±4.98	8.23±5.86
Period of disease<10 yıl (n)	12 (%48)	13 (%52.0)	25 (%62.5)
Period of disease>10 yıl (n)	7 (%46.7)	8 (%53.3)	15 (%37.5)

Disclosure: Nothing to disclose

Sunday, June 21 2015
Autonomic nervous system disorders

P2101
Head-up tilt table test in differentiating neuropathic from hyperadrenergic type of postural orthostatic tachycardia syndrome (POTS)

L. Crnošija[1], M. Krbot Skoric[2], I. Adamec[2], A. Mišmaš[2], V. Miletić[2], R. Šprljan-Alfirev[2], A. Junaković[2], A. Pavelić[1], M. Lovrić[3], M. Habek[2]
[1]School of medicine, University of Zagreb, Zagreb, Croatia, [2]University Hospital Centre Zagreb, Neurology, Zagreb, Croatia, [3]University Hospital Centre Zagreb, Department of Laboratory Diagnostics, Zagreb, Croatia

Background and aims: The aim of this study was to investigate differences between hyperadrenergic and neuropathic type of POTS in cardiovascular response to orthostatic provocation, and to create a diagnostic model that could effectively differentiate between the two, using only head-up tilt table test (HUTT).

Methods: 43 POTS patients (25 women, 18 men) underwent HUTT protocol: 10-minute supine phase and 30-minute 70° tilted phase. Tilted phase ended earlier if vasovagal syncope occurred or patient reported intolerable symptom/s. Serum catecholamine levels were determined in 10th minute of supine and tilted phase, and patients were categorized into one of two types of POTS based on the norepinephrine level in the tilted phase (≥3.5 nmol/L=hyperadrenergic).

Results: 10 patients had hyperadrenergic (group 1) and 33 had neuropathic (group 2) type of POTS. In group 1, 80% of patients were men, and in group 2, 69.7% were women (p=0.005). Group 1 had higher values of heart rate during supine phase (82.6 ±16.3 bpm vs. 73.8 ±10.4 bpm, p=0.048). Group 2 had earlier tilted phase mean ending time (8.8 ±6.8 min vs. 21.2±4.5 min, p=0.001) (Figure 1) and lower values of diastolic blood pressure difference between 1st minute of tilted phase and supine values (-1.7 ±7mmHg vs. 5.6 ±7.5mmHg, p=0.007) (Figure 2). Using observed differences in response to orthostatic provocation we developed a HUTT model for differentiating neuropathic POTS (Figure 3) with sensitivity of 76% and specificity of 80%.

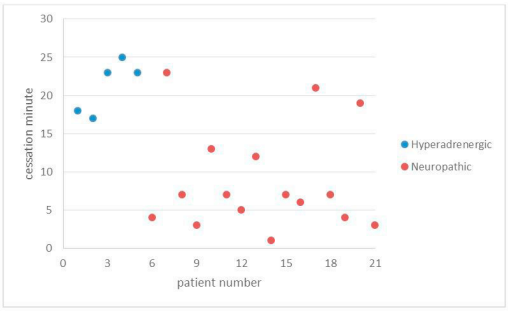

Figure 1 – Distribution of time to cessation of tilted phase of head-up tilt table test depending on type of POTS.

Distribution of time to cessation of tilted phase of head-up tilt table test depending on type of POTS.

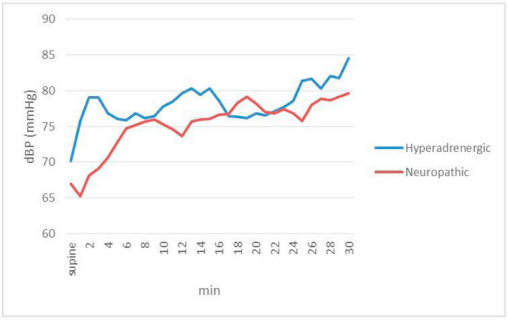

Figure 2 – Dyastolic blood pressure (dBP) changes during head-up tilt table test in patients with hyperadrenergic and neuropathic type of postural orthostatic tachycardia syndrome.

Dyastolic blood pressure (dBP) changes during head-up tilt table test in patients with hyperadrenergic and neuropathic type of postural orthostatic tachycardia syndrome.

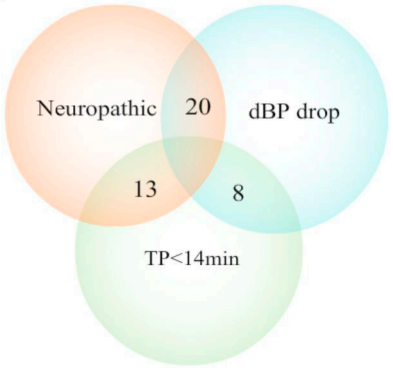

Figure 3 – Venn diagram of HUTT model. dBP drop – average dyastolic blood pressure (AdBP) at 1. minute of tilt phase is lower than AdBP during supine phase. TP<14min – cessation of tilted phase before 14th minute.

Venn's diagram of the proposed model.

Conclusion: Based on these findings it can be concluded that HUTT alone can differentiate between two types of POTS, saving time and resources.

Disclosure: Nothing to disclose

P2102

Traumatic spinal cord injury and 24-hour blood pressure profile during primary rehabilitation

E.M. Hagen[1], J. Vibjerg[2], R.M. Hansen[2]
[1]National Hospital for Neurology and Neurosurgery, Queen Square, Autonomic Unit, London, United Kingdom, [2]Spinal Cord Injury Center of Western Denmark, Regional Hospital of Viborg, Department of Neurology, Vyborg, Denmark

Background and aims: Spinal Cord injury (SCI) may interrupt autonomic pathways leading to disturbed cardiovascular homeostasis. Studies have found that patients with SCI have an increased risk of atherosclerosis as a result of the injury itself. The aim of this study was to investigate how non-invasive 24-hour ambulatory blood pressure measurement can be used in clinical praxis to identify disturbances in blood pressure (BP) regulation in patients with injuries above Th6 during primary rehabilitation, within one year after injury.

Methods: A 24-hour ambulatory BP monitor performed on consecutive patients with traumatic SCI admitted to primary rehabilitation at the Spinal Cord Injury Unit of Western Denmark.

Results: 14 SCI patients were included, 10 men and 4 women, aged 55.5±13.5 years (mean ± SD). Time since injury was 0.4±0.3 years. 6 patients had a complete cervical injury; five had an incomplete cervical injury and three patients a complete thoracic injury. The mean BP was 118/68 mmHg for complete cervical injuries, 134/85 mmHg for incomplete cervical injuries and 133/85 mmHg for complete thoracic injuries during daytime, and 116/64 mmHg, 105/64 mmHg and 124/77 mmHg respectively, during night-time. Systolic BP at night was higher than during the day in 29% of the patients (n=4), and 21% (n=3) were non-dippers. Nocturnal hypertension was present in 21% (n=3).

Conclusion: Ambulatory BP detected a high incidence of reversed dipping and nocturnal hypertension. Ambulatory BP monitoring provides useful information regarding BP during primary rehabilitation.

Disclosure: Nothing to disclose

P2103

Central autonomic dysfunction upon orthostasis as a remainder of traumatic brain injury

M.J. Hilz[1], J. Markus[1], R. Wang[1], S. Moeller[1], T. Intravooth[1], K. Hösl[2], J. Koehn[1]
[1]University of Erlangen-Nuremberg, Department of Neurology, Erlangen, Germany, [2]Klinikum am Europakanal , Department of Psychiatry, Addiction Psychiatry, Psychotherapy and Psychosomatic Medicine, Erlangen, Germany

Background and aims: Patients with a history of traumatic brain injury (post-TBI-patients) have an unexplained increased risk of mortality, possibly due to central autonomic dysfunction (CAD). To evaluate CAD in post-TBI-patients, we assessed cardiovascular-autonomic modulation at rest and upon standing in post-TBI-patients.

Methods: In 20 mild post-TBI-patients (4-78 months post-TBI, 33±13 years, GCS-scores upon injury 13-15), 20 moderate or severe TBI-patients (6-94 months post-TBI, 33±9 years, GCS-scores <13), and 20 age-matched controls (29±10 years), we monitored respiration, RR-intervals (RRI) and systolic blood pressure (BPsys) at supine rest and upon standing. We calculated spectral powers of mainly sympathetic low (LF: 0.04-0.15Hz) and parasympathetic high (HF: 0.15-0.5Hz) frequency RRI-fluctuations, sympathetic LF-powers of BPsys, RRI-LF/HF-ratios, and normalized (nu) LF- and HF-powers of RRI. We correlated autonomic parameters and GCS-scores (Spearman-test), and compared patient and control data while supine and standing (RANOVA; significance: $p<0.05$).

Results: While supine, BPsys and nuRRI-LF-powers were higher, RRI-HF-powers were lower in moderate and severe post-TBI-patients than in mild post-TBI-patients and controls. RRI-LF/HF-ratios were higher in moderate and severe post-TBI-patients than controls. nuRRI-LF-powers were higher, nuRRI-HF-powers were lower in mild post-TBI-patients than controls.

Upon standing, only controls and mild post-TBI-patients increased BPsys and decreased RRI-HF-powers. Only controls increased BPsys-LF-powers. Upon standing, nuRRI-LF-powers, RRI-LF/HF-ratios correlated directly and nuRRI-HF-powers indirectly with GCS-scores.

Conclusion: While supine, TBI-patients had increased sympathetic activity. Upon standing, TBI-patients did not adequately increase sympathetic and reduce parasympathetic modulation. The correlation between GCS-scores and autonomic parameters during orthostasis suggests increased CAD with increased TBI-severity.

Disclosure: The study was partially funded by the International-Brain-Research-Foundation, IBRF, Flanders, NJ, USA.

P2104

Autonomic dysfunction in Alzheimer's disease

C. Jensen-Dahm[1], G. Waldemar[1], T. Jensen[2], L. Malmqvist[3], M.M. Møller[4], B.B. Andersen[1], P. Høgh[5], M. Ballegaard[4]
[1]Rigshospitalet, Danish Dementia Research Centre, Neurology, Copenhagen, Denmark, [2]Aarhus University Hospital, Neurology, Aarhus, Denmark, [3]Rigshopitalet, Clinical Neurophysiology, Copenhagen, Denmark, [4]Rigshospitalet, Clinical Neurophysiology, Copenhagen, Denmark, [5]Roskilde Hospital, Denmark, Roskilde, Denmark

Background and aims: Autonomic function has received little attention in Alzheimer's disease (AD). AD pathology has an impact on brain regions which are important for central autonomic control, but it is unclear if AD is associated with disturbance of autonomic function. We aimed to investigate autonomic function using standardized techniques in patients with AD and healthy age-matched controls.
Methods: 33 patients with mild to moderate AD and 30 age- and gender-matched healthy controls, without symptoms of autonomic dysfunction, underwent standardized autonomic testing with deep breathing, Valsalva maneuver, head-up tilt and isometric handgrip test. Brachial pressure curve and electrocardiogram were recorded for off-line analysis of blood pressure and beat-to-beat heart rate (HR).
Results: AD patients had impaired blood pressure responses to Valsalva maneuver ($p<0.0001$) and HR response to isometric contraction ($p=0.0001$). A modified composite autonomic scoring scale showed greater degree of autonomic impairment in patients compared to controls (patient: 2.1 ± 1.6; controls: 0.9 ± 1.1, $p=0.001$). HR response to deep breathing and Valsalva ratio were similar in the two groups.
Conclusion: We identified autonomic impairment ranging from mild to severe in patients with mild to moderate AD, who did not report autonomic symptoms. Autonomic impairment was mainly related to impairment of sympathetic function. The clinical implications of this finding are that in AD may be associated with autonomic disturbances, but patients with AD may rarely report symptoms of autonomic dysfunction. Future research should systematically evaluate symptoms of autonomic function and characterise risk factors associated with autonomic dysfunction.
Disclosure: Nothing to disclose

P2105

Orthostatic hypotension and antihypertensive drugs

A. Mišmaš[1], A. Bazina[1], M. Krbot Skoric[1], A. Ljilja[2], I. Adamec[1], A. Junaković[1], L. Crnošija[3], M. Habek[1]
[1]University Hospital Center Zagreb, Neurology, Zagreb, Croatia, [2]Clinical Hospital Dubrava, Department of Internal Medicine, Division for Pulmology, Zagreb, Croatia, [3]School of Medicine, Zagreb, Croatia

Background and aims: The aim of this study was to determine how often patients older than 60 years who are diagnosed with orthostatic hypotension (OH) on the tilt-table test are taking antihypertensive medications and what kind.
Methods: Medical records from the Autonomic Nervous system Laboratory, University Hospital Center Zagreb, Zagreb, Croatia were retrospectively reviewed in a period from April 2012 to April 2014 to identify patients older than 60 and diagnosed with OH by the tilt-table test. Data on sex, age, presenting symptoms, antihypertensive drugs and outcome were assessed.
Results: We identified 55 patients that met inclusion criteria, 33 males (60%), 22 females (40%); mean age 70.43 ± 7.79. The most common presenting complaints were transient loss of consciousness (syncope) (56.4%), instability (45.5%) and dizziness (32.7%). Among them 69.1% (N=38) were taking antihypertensive drugs; 30.9% (N=17) were taking 1; 20.0% (N=11) 2; 16.4% (N=9) 3 and 1.8% (N=1) 4 antihypertensive medications. Patients were prescribed with angiotensin-converting-enzyme inhibitors in 34.5%; beta-blockers in 30.9%; diuretics in 27.3%; calcium channel blockers 21.8%; alpha-blockers in 1.8% and other in 10.9% cases. All patients with OH were routinely given advice on antihypertensive drug reduction and dietary measures. Follow-up data were available for 26 (47.2%) patients and 18 (69.2%) reported clinical improvement.
Conclusion: Patients over 60 years with OH often take antihypertensive drugs. Identification of the drugs and their reduction could help prevent iatrogenic OH and its complications.
Disclosure: Nothing to disclose

P2106

The adventure of the Lion's Mane: acute autonomic neuropathy induced by jellyfish toxicity.

R. Lonergan[1], I. McGurgan[2], P. Wiseman[1], J. Duignan[1], E. McGrath[1], S. Connolly[3], C. McGuigan[4]

[1]St. Vincent's University Hospital, Neurology, Dublin, Ireland, [2]Dublin, Ireland, [3]St Vincent's University Hospital, Elm Park, Dublin [4], Ireland, Department of neurophysiology, Dublin, Ireland, [4]St Vincent's University Hospital, Department of Neurology, Dublin, Ireland

Background and aims: Cyanea capillata jellyfish sting may induce autonomic neuropathy.

Methods: A 51-year-old man presented with recurrent postural lightheadedness 3 days subsequent to anaphylactic shock requiring resuscitation. He had developed bronchospasm with collapse hours after a Lion's Mane jellyfish sting whilst swimming. He recalled a minor sting 2 weeks earlier. He also described constipation, erectile dysfunction, urinary hesitancy, and excessive sweating. Examination: afebrile but sweating profusely. Significant postural blood pressure drop (40 mmHg systolic BP) and tachycardia (>100 bpm). Abdomen distended with reduced bowel sounds.

Results: Plain film of abdomen: dilated bowel loops.
ECG: sinus tachycardia.
Nerve conduction studies demonstrated increased thermal thresholds on quantitative sensory threshold testing of feet. R-R interval studies showed loss of variation between normal and deep breathing. Sympathetic skin response was reduced in the feet. Negative screening for other infectious/inflammatory/metabolic/paraneoplastic causes. He was managed conservatively (fludrocortisone), with gradual reduction of symptoms. However, persistent postural lightheadedness after 3 months prompted intravenous immunoglobulin therapy.

Conclusion: Clinical presentation with anaphylaxis and subsequent dysautonomia, with small fibre studies demonstrating involvement of small unmyelinated C fibres, suggested an autonomic neuropathy, likely secondary to cyanea capillata (Lion's Mane) toxin, as previpusly rarely described. In the phylum Cnidaria , a cnidocyte fires a venom-containing cnidocyst. Polypeptide venoms cause ion transport abnormalities at cellular level, release inflammatory mediators, and act as direct toxins on nervous tissue/ autonomic fibres. Associated fatality inspired a Sherlock Holmes story (The Adventure of the Lion's Mane). Awareness of this potential, serious complication may guide initial investigation and inform optimal management post-sting.

Disclosure: Nothing to disclose

P2107

Functional neurological symptoms in patients with postural tachycardia syndrome (PoTS)

L. Ricciardi[1], A.P. Owens[2], G. Ferrazzano[3], V. Iodice[2], C. Mathias[2], M. Edwards[1]

[1]Institute of Neurology, London, United Kingdom, [2]University College London, Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square/Division of Clinical Neurology, Institute of Neurology,, London, United Kingdom, [3]University of Rome, Rome, Italy, Department of Neurology and Psychiatry, 'sapienza', Rome, Italy

Background and aims: Postural tachycardia syndrome (PoTS) is characterized by an increase in heart rate >30 beats per minute (BPM) within 10 minutes of standing, or a maximum HR >120 BPM without orthostatic hypotension while standing. PoTS is often included in the differential diagnosis of chronic unexplained symptoms. Many patients with PoTS present comorbid functional somatic disorders, such as functional gastrointestinal or bladder disorders. To date no data are available regarding the co-occurrence of functional neurological symptoms (FNS) in these patients.

Aim: We retrospectively investigated the presence of FNS in consecutive patients referred to our London-based national referral centre for autonomic disorders over a three-year period.

Methods: We reviewed the medical records of all consecutive patients referred for suspected dysautonomia between 2012 and 2014 who received a diagnosis of PoTS. We evaluated all cases for a diagnosis of FNS. We describe demographic and clinical characteristics of this population.

Results: We identified 559 patients with PoTS (F/M: 500/59, mean age 36.0±11.4). Within this population, 33(6%) patients also received a diagnosis of FNS (F/M: 2/33, mean age 35.8±10.1). Non-epileptic attacks and muscle jerks/spasm/twitches were the most frequent clinical presentation of FNS, each occurring in 27% (9/33) of the PoTS/FNS cases. Functional tremor was present in 18% (6/33), functional dystonia in 9% (3/33), functional weakness in 15% (5/33) and sensory symptoms in 1 patient.

Conclusion: Our results confirm that PoTS mainly occurs in young, female patients. FNS can co-occur with PoTS, with non-epileptic attacks and functional movement disorders the most frequent clinical manifestations.

Disclosure: Nothing to disclose

P2108

Autonomic vasomotor dysfunctions In hand-arm vibration syndrome

Z. Stoyneva
Clinic of Occupational Diseases, Department of Neurology, Sofia, Bulgaria

Background and aims: Peripheral nervous, vascular and musculoskeletal disorders of the upper limbs are characteristic for hand-arm vibration syndrome (HAVS).
AIM: to assess laser Doppler-recorded microcirculatory reactivity in hand-arm vibration syndrome patients.
Methods and Materials: Skin fingerpulp perfusion (PU) was monitored of 20 patients with HAVS and 15 healthy controls as initial values and during heating test (up to 440 C) and venoarteriolar posture test (with hands on the sternum and in dependency) by laser Doppler system PeriFlux 4001 Master and PeriTemp4005 Heater (PERIMED, Stockholm, Sweden). Data were analyzed by Wilcoxon matched pairs signed rank test and Mann-Whitney U test for unpaired data by SPSS software package with level of significance $p<0.05$.
Results: The values of the initial mean perfusions in the HAVS patients were significantly lower compared to the healthy controls. Lower skin perfusions to local heating were measured due to significantly reduced microvascular responses and vasodilator thermal induced capacity in the patients compared to the healthy controls ($p<0.0001$). Abnormal venoarteriolar reflex responses with lacking or decreased perfusion reduction in hand dependency was established in HAVS patients due to local vasomotor dysfunction induced either by postganglionar sympathetic insufficiency with vascular tone failure or/and altered smooth muscle cells' responses.
Conclusion: Microcirculatory and autonomic vasomotor dysfunctions were found in HAVS patients. Laser Doppler flowmetry applied with functional tests is a reliable quantitative noninvasive method for investigation of skin microcirculation and microvascular dysregulations.
Disclosure: Nothing to disclose

P2109

Wavelet analysis to differentiate dementia patients with and without autonomic dysfunction

W. Struhal[1], C. Mahringer[2], H. Lahrmann[3], P. Buhl[2], G. Ransmayr[1]
[1]Kepler University Clinic, Department for Neurology and Psychiatry, Linz, Austria, [2]Kepler University Clinic, Department for Medical Engineering, Linz, Austria, [3]Vienna, Austria

Background and aims: Recent data suggest a high incidence of autonomic dysfunction in patients suffering Alzheimer's disease (AD) and Frontotemporal Dementia behavioural variant (bvFTD). The standard tests to investigate cardiovascular function are time consuming and require compliance. Biomarker, which are easier to obtain with less compliance needed, would be of interest. This study evaluates the value of wavelet analysis of heart rate variability (HRV) data to differentiate dementia patients from dementia patients without autonomic involvement.
Methods: Patients were prospectively enrolled at the Department of Neurology and Psychiatry, AKH Linz. Patients were first evaluated employing standard autonomic tests (Ewing battery) and divided into 2 groups: A unremarkable cardiovascular autonomic results, B pathologic cardiovascular autonomic results. HRV data derived from ECG recordings in supine and upright position (passive head up tilt test) were analysed using Morlet wavelets and results compared between both groups.
Results: 28 patients were included (17 group A: 64.53 ±10.04 years, 4 male, 13 female and 11 group B with autonomic dysfunction: 75.91±6.82 years, 3 male, 8 female). Group A showed significantly increased sympathetic power during orthostasis (+7.7% resulting in a sympathetic proportion of 86% of total autonomic power) whereas group B showed no significant autonomic modulation during orthostatic stress.
Conclusion: Patients with AD and bvFTD show a high incidence of impaired cardiovascular regulation during tilt test. Wavelet analysis of HRV in supine and upright position seems valuable for the evaluation of autonomic involvement in this patient group and does not require compliance from the patient.
Disclosure: This study was funded by the National Bank of Austria (OeNB grant 13240).

P2110

Eyeball pressure stimulation shows paradox sympathetic activation in patients after moderate and severe traumatic brain injury

R. Wang[1], T. Intravooth[1], S. Moeller[1], J. Koehn[1], F. Aurnhammer[2], H. Marthol[1], M.J. Hilz[1]

[1]University of Erlangen-Nuremberg, Department of Neurology, Erlangen, Germany, [2]Waldkrankenhaus St. MarienGmbH, Department of Internal Medicine I and IV, Erlangen, Germany

Background and aims: Long-term mortality is increased in patients with a history of traumatic brain injury (TBI). The unknown pathophysiology might be related to central-autonomic-network dysfunction compromising cardiovascular regulation. In patients with a history of TBI, eyeball-pressure-stimulation (EPS), a parasympathetic cardiovascular challenge, might uncover autonomic-dysfunction. In patients with a history of moderate or severe TBI, we determined whether EPS shows autonomic-cardiovascular-dysregulation.

Methods: In 25 moderate-TBI-patients (33.00±10.23 years, 3 to 120 months post-injury), 26 severe-TBI-patients (32.42±10.93 years, 5 to 144 months post-injury), and 30 controls (29.13±9.77 years), we recorded respiration, RR-intervals (RRI), systolic and diastolic blood-pressure (BPsys, BPdia), before and during EPS (120seconds; 30mmHg), using an ophthalmologic ocular-pressure-device (Okulopressor®). We calculated spectral-powers of mainly sympathetic low (LF: 0.04-0.15Hz) and parasympathetic high (HF: 0.15-0.5Hz) frequency RRI-fluctuations, sympathetically mediated LF-powers of BPsys, and RRI-LF/HF-ratios, and calculated normalized (nu) LF- and HF-powers of RRI. We compared parameters between groups before and during EPS by RANOVA with post-hoc analysis (significance: $p<0.05$).

Results: At rest, severe-TBI-patients had lower LF-BPsys-powers than the controls. During EPS, only controls significantly increased RRIs and HFnu-RRI-powers, and decreased LF-RRI-powers, LFnu-RRI-powers, RRI-LF/HF-ratios, and LF-BPsys-powers. Moderate and severe post-TBI-patients significantly increased BPsys without changing any other parameter.

Conclusion: Even at rest, autonomic BP-modulation is compromised in severe-post-TBI-patients. During EPS, moderate- and severe-post-TBI-patients fail to activate parasympathetic cardiovascular modulation but show paradox sympathetic activation. This central-autonomic- dysregulation might contribute to cardiovascular fatalities.

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P2111

Drip and ship paradigm in acute ischemic stroke: meta-analysis of safety and efficacy

A.C.G. Fonseca[1], M.A. Santos[2]
[1]MOSCAVIDE, Portugal, [2]Hospital de Santa Maria, Neurology, Lisbon, Portugal

Background: The sooner the treatment with intravenous alteplase is started in acute ischemic the higher the probability of a better outcome. One of the possible strategies to decrease time until start of treatment and increase the number of patients receiving alteplase is the "Drip and Ship paradigm". In this approach the administration of intravenous alteplase begins in the nearest hospital followed by immediate transfer to a stroke unit.

Aim: Meta-analysis of "drip and ship" efficacy and safety in acute ischemic stroke

Methods: Systematic review of PUBMED, EMBASE and Cochrane CENTRAL. Clinical trials or observational case-control studies that compared in patients with acute ischemic the start of intravenous alteplase in the nearest hospital followed by transfer to a stroke unit versus the start of treatment with intravenous alteplase in a stroke unit were included. In order to evaluate efficacy, the functional status at hospital discharge and 3 months after stroke was used (independence=Rankin<3). To analyze safety, in-hospital mortality and symptomatic intracerebral hemorrhage were evaluated.

Results: From 94 studies, nine observational case-control studies were included with a total of 2200 patients. There was not a statistical significant difference regarding the functional status at the time of hospital discharge OR 0.82 95%CI (0.53-1.28) or at 3 months OR 1.22 95%CI (0.75-1.97), symptomatic intracerebral hemorrhage OR 0.82 95%CI (0.53-1.28) or in-hospital death OR 1.02 95%CI (0.74-1.41).

Conclusion: Published studies did not show a statistical significant difference regarding safety or efficacy of drip and ship versus beginning of treatment with intravenous alteplase at a stroke unit.

Disclosure: Nothing to disclose

P2112

Hemostasis and hemorheology in acute ischemic stroke after i.v. thrombolysis

M. Gafarova[1], M. Domashenko[1], M. Maximova[1], A. Shabalina[2], M. Kostyreva[2], D. Korobkova[1], R. Konovalov[3]
[1]Research Center of Neurology, ASU, Moscow, Russian Federation, [2]Research Center of Neurology, Hemostasis and Hemorheology, Moscow, Russian Federation, [3]Research Center of Neurology, Radiology, Moscow, Russian Federation

Background and aims: Devastating effect of ischemic stroke (IS) is associated with impaired brain perfusion. Intravenous thrombolysis (IVT) may restore blood flow in large vessels and is believed to be able to improve microcirculation. Hemostatic and hemorheological changes might be essential for microcirculation in IS. The aim of the study was to evaluate the hemostasis and hemorheology in patients with IS treated with IVT and their associations with brain perfusion.

Methods: 70 patients (48M, 22W, mean age 61[54;69]) admitted with acute IS at first 4,5 hours after stroke onset were treated with IVT. Patients underwent neurological examination and blood tests before and after IVT and at 1st, 7th, 21st day after IVT. Determination of hemostatic and hematological parameters, kinetics of erythrocyte aggregation/disaggregation and erythrocyte deformability, evaluation of platelet aggregation (PA) were conducted. CT-angiography, CT-perfusion, MRI of the brain were performed before and after IVT to identify occlusion/recanalization and to measure the size of penumbra and infarct core (IC).

Results: Adrenaline-induced PA was significantly higher in patients without recanalization after thrombolysis and severe neurological deficit (NIHSS>14) after IVT. Decreased prothrombin time was associated with larger IC at first 24 hours and more severe neurological deficit at 7 and 21 day. High leucocyte level and low lymphocyte level were measured at 1st day in patients with larger IC, higher NIHSS score and worse functional outcome. There was no correlation of measured hemorheological and hemostatic parameters with penumbra size.

Conclusion: Hemostatic and hematological disturbances are associated with infarct core size and clinical features in patients with IS after IVT.

Disclosure: Nothing to disclose

P2113

Poor short-term outcome in patients with ischemic stroke and active cancer

T. Gattringer[1], M. Kneihsl[1], C. Enzinger[1], G. Wünsch[2], M. Khalil[1], T. Urbanic-Purkart[1], F. Payer[1], K. Niederkorn[1], F. Fazekas[1]

[1]Medical University of Graz, Neurology, Graz, Austria, [2]Medical University of Graz, Medical Informatics, Statistics and Documentation, Graz, Austria

Background and aims: In our aging society, ischemic stroke and cancer often co-occur. It is often difficult to decide if this relationship is etiologically linked (such as from presumed procoagulatory carcinoma effects) or a chance finding and how it affects stroke outcome. In this work we examined clinical, neuroimaging and prognostic aspects of acute ischemic stroke (AIS) patients with known active cancer compared to AIS patients with stable malignoma.

Methods: All AIS patients that were admitted to the neurological department of our primary and tertiary care university hospital between 2008 and 2014 were identified (n=4918). Of those, 319 patients had an additional diagnosis of cancer. Cancer patients were divided in "active cancer" (metastasis, ongoing chemo- or radiation therapy, n=73) and "non-active cancer" (remission, n=227) groups. The level of significance was set at $p<0.05$.

Results: Patients with active cancer were significantly younger (70.3±10.6 vs. 74.9±9.9 years), had more severe stroke syndromes (NIHSS: median 5 versus 3), more frequently cryptogenic strokes (50.7 vs. 32.5%) and more often infarcts in multiple cerebrovascular territories (26 vs. 5%) compared to patients with malignancies in remission. In-hospital mortality (median stay of 9 days) was significantly increased in patients with active cancer (21.9 vs. 6.1%).

Conclusion: Our findings of a high proportion of cryptogenic stroke and infarcts in multiple vascular territories in AIS patients with concomitant active cancer support the role of active malignancies in stroke etiology. Furthermore, this combination appears to entail a bad short-term prognosis even in the wake of at first relatively mild stroke syndromes.

Disclosure: Nothing to disclose

P2114

Platelet receptor expression in patients with atherothrombotic and lacunar stroke

V. Goldobin[1], E. Klocheva[1], O. Sirotkina[2], T. Vavilova[3]

[1]NWSMU n.a. I.I.Mechnikov, Neurology, StPetersburg, Russian Federation, [2]StPINP n.a. B.P.Konstantinov, Gatchina, Russian Federation, [3]NWSMU n.a. I.I.Mechnikov, StPetersburg, Russian Federation

Background and aims: Platelet receptors are crucial for interaction between platelets and endothelial cells. Main platelet receptors are IIb/IIIa (fibrinogen) and 1b (vonWillebrand factor). Their expression is essentially important in patients with atherothrombotic stroke (ATS) and lacunar infarction (LI).

Methods: 48 patients with ATS (27 men, 21 women, age–66.1±10.4 years), 47 patients with LI (23 men, 24 women, age–66.7±10.1 years) were examined during acute stage. We included patients with benign and uncomplicated course of stroke. Neurological examination, neurovisualisation, duplex scanning of brachiocephalic arteries, routine laboratory tests were performed. Flow cytometry was performed on day 9-11 of stroke onset. We used flow-cytometer CYTOMICS FC500 (Beckman Coulter, US) for detection of IIb/IIIa and α-chain of 1b receptor with fluorescent labeled antibodies CD61-FITC and VM16d-FITC.

Results: There was no difference in fibrinogen receptor expression upon platelets in men vs women with ATI and LI (both basal and adenosindiphosphate stimulated).

Density of GP1b upon platelet surface in men with LI was significantly higher compared with men with ATI (5.4±3.1 vs. 4.0±1.3, $p<0.05$).

In women with ATS there was direct correlation between 1b expression and NIHSS score on day 30 ($r=0.769$, $p<0.05$). There was no such correlation in women with LI or in men with both ATI and LI.

Conclusion: Difference in expression of vonWillebrand factor receptors on platelets, connected with gender and pathogenetic type of stroke was revealed. Mechanisms underlying such findings might be explored for specified antiplatelet therapy because effectiveness of current antiplatelet therapy is not sufficient.

Disclosure: Nothing to disclose

P2115

Intracranial hemorrhage after non-urgent carotid recanalization: a hyperperfusion syndrome with devastating consequences

M. Gonzalez Delgado[1], R. García[2], E. Murias[3], P. Vega[3], E. Morales[3], M. Alonso[3], L. Camblor[3], S. Calleja[3]
[1]Oviedo, Spain, [2]Centro Médico de Asturias, Oviedo, Spain, [3]Hospital Universitario Central de Asturias, Oviedo, Spain

Background and aims: Hyperperfusion syndrome has been described as the triad of headache, neurological deficit and seizures developing after carotid revascularization associated with hypertension and in the absence of cerebral ischemia. Intracranial hemorrhage is the most serious manifestation of cerebral hyperperfusion.

Methods: Consecutive patients who needed non-urgent internal carotid artery (ICA) recanalization, carotid stenting (CAS) or carotid endarterectomy (CEA) were studied from February 2005 to November 2014.

Results: 957 patients were studied. 6 of them (5 males and one female) presented ICH after ICA recanalization (CAS). Mean age was 71.6 (54-84) years. 4 patients presented as clinically symptomatic carotid pathology and 2 as asymptomatic. Cranial CT at admission showed leukaraiosis in 2 patients, was normal in 2. A borderline ischemic stroke was seen in a further 2 patients. At the time of the procedure, 4 patients were under ASA. Another 2 were under Clopidogrel and LMWH (nadroparin 0.8/24h). One was under nadroparin 0.6/24h and another under nadroparin 0.4/24h. Further 2 patients were under ASA and clopidogrel. After the procedure, 4 patients presented with neurological worsening, one patient with a slight headache and another with transient neurological deficit prior to a decrease in the level of consciousness. Cranial CT showed an ipsilateral ICH in all cases. Half of the patients died.

Conclusion: ICH after non-urgent carotid recanalization had a poor prognosis. Neurological symptomatology related with such may be trivial, namely, a slight headache. A careful antithrombotic treatment should be recommended, and high LMWH doses should be avoided.

Disclosure: Nothing to disclose

P2116

Thoracic aortic calcification is associated with incident stroke in the general population in addition to established risk factors

D.M. Hermann[1], N. Lehmann[2], J. Gronewold[1], M. Bauer[3], A.A. Mahabadi[3], C. Weimar[1], K. Berger[4], S. Moebus[2], K.-H. Jöckel[2], R. Erbel[3], H. Kälsch[3]
[1]University Hospital Essen, Neurology, Essen, Germany, [2]Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany, [3]University Hospital Essen, Cardiology, Essen, Germany, [4]Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany

Background and aims: The aorta is a major source of cerebral thromboembolism, but its role in stroke pathogenesis is not well understood. We examined whether thoracic aortic calcification (TAC), a marker of aortic plaque load, is associated with stroke in addition to established risk factors.

Methods: A total of 3930 subjects from the population-based Heinz Nixdorf Recall study (45-75 years; 47.1% men) without previous stroke or coronary heart disease were evaluated for incident stroke events over 109.0 ± 23.3 months. Cox proportional hazards regressions were used to examine associations with stroke of TAC in addition to established risk factors (age, sex, systolic blood pressure, LDL, HDL, diabetes, and smoking).

Results: 101 incident strokes occurred during the follow-up period. Subjects suffering a stroke had significantly higher TAC values at baseline than the remaining subjects (median =83.1 [Q1;Q3 =4.7;472.9] vs. 15.7 [0.0;117.1]; P<0.001). In a multivariable Cox proportional hazards regression, log (TAC + 1) (hazards ratio [HR] =1.09 [95% confidence interval =1.00-1.19]; P=0.044) was associated with stroke. Further analyses revealed that log (DTAC+1), i.e. calcification of the descending aorta (1.11 [1.02-1.20]; P=0.016), but not log (ATAC + 1), i.e. calcification of the ascending aorta (1.02 [0.93-1.11]; P=0.713), was associated with stroke.

Conclusion: Calcification of the thoracic aorta, more specifically its descending segment, is associated with incident stroke in addition to established risk factors.

Disclosure: Nothing to disclose

P2117

Paracrine protective effects of HMGB1 in ischemic oligodendrocyte death

J.Y. Choi[1], H.W. Lee[2], B.G. Kim[3]
[1]Ajou University School of Medicine, Neurology, Suwon, Korea, Republic of, [2]Ewha Womans University School of Medicine, Neurology, Seoul, Korea, Republic of, [3]Suwon, Korea, Republic of

Background and aims: Ischemic white matter injury is commonly encountered in clinical practices. Demyelination with oligodendrocyte (OL) loss is a prominent histopathological feature. Therefore, protection of OLs from ischemic insults would be an important therapeutic strategy to overcome cognitive impairments caused by ischemic white matter injury. Previously, we found that Toll-like receptor 2 (TLR2) expressed in OL lineage cells provides cell-autonomous protective effects. Here, we identified High-mobility Group protein B1 (HMGB1) as an endogenous TLR2 ligand to promote protective effect in ischemia-induced OL death.

Methods: Cultured primary OLs were exposed to oxygen-glucosed deprivation (OGD). The death of OLs was measured by LDH assay. The amount of HMGB1 ih the conditioned media (CM) was measured by Western blot and the protective activity of CM with or without immunodepletion was tested. For in vivo ischemic demyelination model, endothelin was injected into unilateral internal capsule. Neurobehavioral recovery was measured by the corner test and the pole test.

Results: OLs under OGD released HMGB1 into bathing media. CM collected from OLs exposed to OGD exhibited protective activity against OGD-induced OL death in a TLR2-dependent manner. Immunodepletion of HMGB1 from the conditioned media abolished the protective activity.Application of glycyrrhizin, a specific HMGB1 inhibitor, resulted in the aggravation of OGD-induced OL death. Animals with glycyrrhizin co-injection showed worsening neurobehavioral parameters in endothelin-induced white matter stroke model. The behavioral deficits were accompanied by expansion of demyelinating lesion by glycyrrhizin.

Conclusion: These results suggest that HMGB1 may act as an endogenous TLR2 ligand mediating protective effects on OLs after ischemic insult.

Disclosure: Nothing to disclose

P2118

Delirium in the stroke unit – preliminary study on Polish population

E. Klimiec[1], P. Moskal[2], K. Kowalska[1], P. Potoczek[1], A. Srednicka[3], K. Ochyra[3], M. Kornas[4], A. Słowik[5], A. Klimkowicz-Mrowiec[5]
[1]Department of Neurology, University Hospital in Krakow, Cracow, Poland, [2]University Hospital in Krakow, Cracow, Poland, [3]Jagiellonian University Medical College, Cracow, Poland, [4]The Institute of Applied Psychology, Jagiellonian University, Cracow, Poland, [5]Department of Neurology, Jagiellonian University Medical College, ul. Botaniczna [3], [31-503] Krakow, Poland, Cracow, Poland

Background and aims: Delirium occurs in 10-48% of patient in the acute phase of stroke. The occurrence highly depends on population and model of care. Knowledge about predisposing factors may be helpful in identifying patients at the highest risk of delirium. There were no studies on delirium in stroke units in countries of Central or Eastern Europe. We aimed to assess occurrence and predisposing factors for delirium after stroke or TIA in Polish population.

Methods: Consecutive patients admitted to the Stroke Unit, Department of Neurology, University Hospital, Krakow, with ischemic or haemorrhagic stroke or TIA were included in the study. Included patients were assessed on daily basis during the first week, DSM-V criteria were used for delirium diagnosis. Information on demographical, medical, and stroke-related predisposing factors were collected.

Results: 267 consecutive patients were included: 219 with ischemic stroke, 26 with haemorrhagic stroke and 22 with TIA. Delirium was observed in 21% of patients (n=57); 12% (n=7) had hyperactive, 44% (n=25) hypoactive and 44% (n=25) mixed subtype of delirium. Age (p=0.0001), use of anticholinergic drugs (p=0.036), cognitive impairment (p=0.025), infections (p=0.0001), neglect (p=0.008), visual impairment (p=0.0001), higher severity of stroke (p=0.003) and stroke in anterior or posterior circulation (p=0.025) were identified as a risk factor for post-stroke delirium.

Conclusion: One in five patients developed delirium during the first week of hospitalization. Almost half of them presented with hypoactive type, which is difficult to diagnose. Therefore, active screening should be implemented in routine practice, especially in predisposed patients.

Disclosure: Nothing to disclose

P2119

A meta-analysis of stentrievers versus other treatment modalities in mechanical thrombectomy for stroke

A. Kobayashi[1], M. Pedracka[2], A. Czlonkowska[1]
[1]Institute of Psychiatry and Neurology, 2nd Department of Neurology, Warsaw, Poland, [2]Wyszynski Specialist District Hospital, Department of Neurology, Lublin, Poland

Background and aims: Mechanical thrombectomy has proved to be effective in management of ischaemic stroke with large artery occlusion in a large pragmatic trial – MR CLEAN, in which stentrievers were predominantly used. Previous neutral trials have allowed the use of different approaches including the MERCI and Penumbra devices, intraarterial thrombolysis, etc. and only 3.4% of patients were treated with a stentriever.

The aim of this study is to systematically review and meta-analyze the results of controlled studies of stentrievers versus other endovascular treatment (EVT) modalities.

Methods: A literature search of studies of mechanical thrombectomy with stentrievers versus other EVT approaches has been performed and results defined as recanalization rates, mortality and death or disability defined as a mofified Rankin score (mRS) 3-6 at 3 months metaanalyzed.

Results: 4 studies which included 561 patients in total (277 treated with stentrievers and 284 with other EVT) have been identified. The recanalization rates using stentrievers versus other EVT were 76.2% and 52.1%, respectively ($p<0.001$). Death or disability at 90 days was 35.9% versus 56.3%, respectively ($p<0.001$). 3 of the trials have analyzed death as an endpoint. The mortality rates were 22.6% versus 30.9%, respectively, showing a non-significant trend ($p=0.07$) towards reduced death rates in patients treated with a stentriever.

Conclusion: Stentrievers showed a higher recanalization rate correlating with a lower chance of death or disability and a trend towards lower mortality. Combined with the results of MR CLEAN it is apparent that stentrievers are superior to other EVT and should be reference standard.

Disclosure: Adam Kobayashi has received travel grants from Balt Extrusion and Covidien/EV3

Child and developmental neurology 1

P2120

POLR3A mutation: a rare cause of hypomyelinating leukodystrophy

S. Mrabet[1], I. Kraoua[1], I. Dorboz[2], H. Ben Rhouma[1], H. Klaa[1], N. Ben Achour[1], A. Rouissi[1], S. Abdelhak[3], O. Tanguy[2], I. Ben Youssef Turki[1]
[1]National Institute Mongi Ben Hmida of Neurology, Department of Child and Adolescent Neurology, Tunis, Tunisia, [2]Robert Debré Hospital, Department of pediatric Neurology, Paris, France, [3]Pasteur Institute of Tunis, Laboratory of Biomedical Genomics and Oncogenetics, Tunis, Tunisia

Background and aims: Mutations in gene encoding the subunit A of RNA polymerase III (POLR3A) have been recently identified as genetic causes of hypomyelinating disorders. POLR3A mutations cause three rare and overlapping leukodystrophy phenotypes: tremor-ataxia with central hypomyelination (TACH), leukodystrophy with oligodontia (LO) hypomyelination, hypodontia and hypogonadotropic hypogonadism (4H) syndrome.

Case Report: We report on a Tunisian girl with TACH phenotype due to POL3A mutation.

Results: A 6-year-old girl was born to consanguineous parents. She had a similar illness as her brother who deceased at the age of 5 years. She had a normal psychomotor development. At age of 15 months, she presented unsteady gait. At 3 years, she developed tremor and at the age of 6 years, she presented school difficulties mainly on speech production and writing. Neurological examination (6 years) showed no mental retardation, nystagmus and cerebellar ataxia with action and intention tremor. She had no dental abnormalities and no signs of hypogonadism. Brain MRI showed diffuse hypomyelination with involvement of U fibers. Fundus examination was normal. Sequence analysis identified a mutation of POLR3A (c.2011T>C, p.Trp671Arg).

Conclusion: POL3A mutations should be evoked in patients with hypomyelination and early onset progressive cerebellar ataxia even in the absence of oligodentia and hypogonadism. Deep white matter hypomyelination is the MRI hallmark of this entity. Hypoplastic corpus callosum, involvement of pallidi and cerebellar atrophy are suggestive but lack in our patient. The identified mutation had been reported once in siblings of Mediterranean origin, born to consanguineous parents suggesting the possibility of a founder mutation.

Disclosure: Nothing to disclose

P2121

Sjögren–Larsson syndrome in a Tunisian cohort

S. Mrabet[1], I. Kraoua[1], I. Dorboz[2], H. Ben Rhouma[1], H. Klaa[1], N. Ben Achour[1], A. Rouissi[1], S. Abdelhak[3], O. Tanguy[2], I. Ben Youssef Turki[1]
[1]National Institute Mongi Ben Hmida of Neurology, Department of Child and Adolescent Neurology, Tunis, Tunisia, [2]Robert Debré Hospital, Department of pediatric Neurology, Paris, France, [3]Pasteur Institute of Tunis, Laboratory of Biomedical Genomics and Oncogenetics, Tunis, Tunisia

Background and aims: Sjögren–Larsson syndrome (SLS) is a rare autosomal recessive neurocutaneous disorder caused by mutations in ALDH3A2, which encodes fatty aldehyde dehydrogenase (FADH). This genodermatosis is characterized by congenital ichthyosis, mental retardation and spastic paraplegia or tetraplegia. We report on clinical and neuroimaging characteristics of SLS in 5 Tunisian patients.

Methods: Retrospective study over 10 years (2004-2014) including 5 patients with SLS. Clinical and imaging data were analyzed.

Results: 5 patients (4M/1F) from three families were included. Mean age of patients was 6.2 years. All patients presented with congenital ichthyosis and developed spastic paraplegia and mental retardation. Generalized dystonia and postural tremor was described respectively in one patient. Brain MRI was performed in 4 patients and showed T2 hypersintensity in the peri-trigona, brainstem and semi oval centers white matter. Proton magnetic resonance spectroscopy was made in 2 patients and showed abnormal peak compatible with lipid content. Ophthalmologic examination showed maculopathy with microcrystals, keratoconjunctivitis and erythematous blepharitis in 2 patients. Diagnosis of SLS was confirmed by enzymatic assay in one patient and by genetic analysis in 4.

Conclusion: We report on 5 patients with typical clinical presentation. The association of movement disorders in 2 patients is uncommon. Indeed, dystonia was reported once and tremor has not been reported before. Spectroscopy reveals specific peak of lipids that make this noninvasive technique useful for the diagnosis of SLS. Classical clinical and imaging presentation of SLS is sufficient to directly analyze the ALDH3A2 gene to confirm diagnosis and to allow genetic counseling.

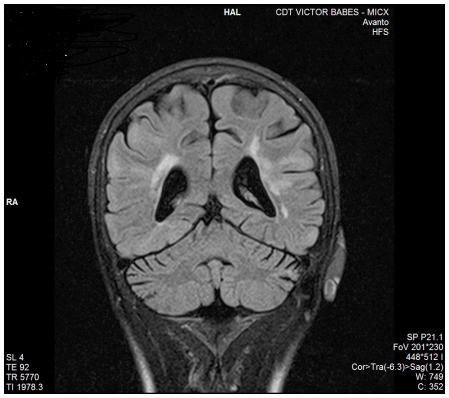
Disclosure: Nothing to disclose

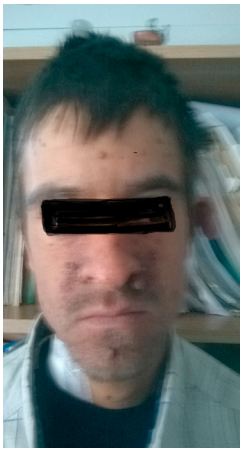
P2122
Atypical presentation of Bourneville Disease

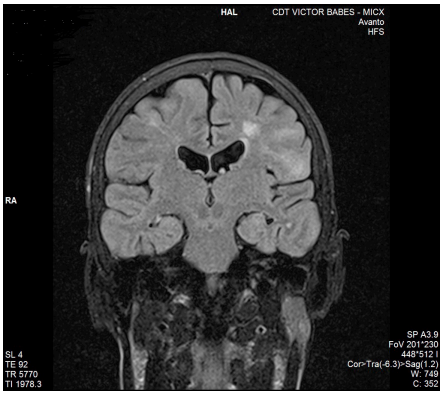
A. Roceanu[1], O. A. Bajenaru[2]
[1]Bucharest, Romania, [2]University Emergency Hospital Bucharest, Neurology, Bucharest, Romania

Background and aims: Tuberous sclerosis (Bourneville Disease) is a congenital disease due to hyperplasia of ectodermal and mesodermal cells from the skin, nervous system, heart, kidney and other organs. The disease is inherited in autosomal dominant mode. Two tumor supressor genes were identified: TSC1 (9q34) who produce hamartin and TSC2 (16013.3) that produces tuberin. Clinically it is characterized by the triad adenoma sebaceum, epilepsy and mental retardation

Case Report: We present the case of a 27-year-old patient who developed renal failure in the l;ast 6 monts, with dialysis treatment. He was referred to our clinic because he experienced an epileptic seizure (a simple partial seizure). The neurological interictal examination was normal. No mental retardation was disclosed. EEG showed bilaterally epileptiform discharges. A native cerebral CT demonstrated periventricular calcific lesions and cerebral IRM revealed 2 subependymal giant cell astrocytoma (SGCA) localized in the cerebral ventricules, near Monro foramen, supporting the diagnosis of tuberous sclerosis. The general examination disclosed facial adenoma sebaceum. ECG and echocardiography were normal. Toraco-abdominal CT scan - ruled out tumor of the kidney or other organs. Patient started everolimus (votubia) and anticonvulsant treatment.







Results: Clinical presentation and neuroimaging features were diagnosed Bourneville Disease. The particularity of the case is the lack of mental retardation and the limited seizure activity. No renal angiomyolipomas were found, the renal failures was due to glomerulonephritis.

Conclusion: TSC is a rare disease with a variable clinical presentation.

Disclosure: Nothing to disclose

P2123
Abstract cancelled

P2124

Early epileptic encephalopathy and aetiological investigation – How far to go?

J. Tomás[1], C. Robalo[1], P. Garcia[2], I. Fineza[1], M. Barbosa[3], P. Maciel[3]

[1]CHUC, Pediatric Unit, Neurology, Coimbra, Portugal, [2]CHUC, Pediatric Unit, Metabolic diseases, Coimbra, Portugal, [3]School of Health Sciences, University of Minho, Life and Health Sciences Research Institute, Braga, Portugal

Background and aims: Early epileptic encephalopathies (EE) are severe neurologic conditions characterized by drug-resistant epileptic seizures and development delay/regression. Multiple aetiologies are involved, including a recently described mutation on SLC35A2 gene, which codes a UDP-galactose transporter, inducing to a congenital disorder of glycosylation (CDG) type II. This mutation causes systemic symptoms, including commonly EE by CNS involvement.

Case Report: Male patient, 8-year-old actually. Followed in outpatient consultation since 10-months-old for polymorphic seizures, severe delayed psychomotor development and acquired microcephaly. He had dysmorphic face, poor visual contact, hypotonia and stereotypies of the extremities .

Results: Metabolic investigation and genetic studies for karyotype, Angelman and Rett syndromes (MECP2) molecular studies were normal. DNA leukocyte exome sequencing revealed hemizygous pathogenic variant for SLC35A2 gene, also present on skin fibroblasts. His mother was heterozygote for this variation. Test for CDG (carbohydrate-deficient transferrin levels) was normal. The patient was treated with sodium valproate, levetiracetam, benzodiazepines and rufinamide, without benefit. He is actually proposed for treatment with ketogenic diet.

Conclusion: We reported a case of EE that began in the first year of life, with a hemizygous pathogenic variant of SLC35A2 gene, inherited from the mother. EE associated with SLC35A2 variations were recently described and are still rare.

Disclosure: Nothing to disclose

P2125

Developmental chick neuronal activity measurement using silk fexible electrode

K. Torimitsu, T. Sonobe, Y. Takizawa, H. Takahashi, S. Watanabe

Tohoku Univ, Sendai, Japan

Background and aims: Continuous measurement of neural activity is important for understanding developmental changes of neurons. Flexible electrode is one of the ideal solution for long-term measurement of neural activity. We previously reported the electrical activity measurement using conductive polymers, such as PEDOT-PSS (poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate)) with multielectrode array. It improves sensitivity and stability of the electrode. Here we use this conductive polymers to silk fibers to form flexible silk electrodes.

Methods: Pristine silk fibers were modified with conductive polymers for chick neural activity measurement. They were inserted in the brain and the tissue of mouse and chick after anesthetized. Developmental changes of their neural activities and their muscle activities were investigated.

Results: Spontaneous beta waves were recorded depending on the development. Number of events and frequencies were changed on delevelopment. Evoked responses were also measured. As the conductive silk electrode is flexible and bio-compatible, long-term measurement could be possible.

Conclusion: The conductive silk electrode allows us sustainable activity monitoring. Long-term implantation of the electrode to the tissue indicates stable measurement capability. It would be a useful tool for in vivo analysis, such as develoment and free-moving behavior.

Disclosure: This work was performed in part under the knowledge based Medical Device Cluster, Miyagi, Japan, Regional innovation Strategy Support Program, MEXT

Education in neurology

P2126

Work engagement during Neurology residency: results from the Attica Study

P. Zis[1], A. Artemiadis[2], M. Lykouri[1], S. Xirou[3], A. Roussopoulou[1], E. Papageorgiou[4], E. Bakola[5], P. Iliopoulos[6], I. Stavropoulos[7], S. Katsavos[8], F. Anagnostopoulos[9]

[1]Evangelismos General Hospital, Neurology, Athens, Greece, 2417 General Military Hospital Nimts, Neurology, Athens, Greece, [3]Eginition University Hospital, Neurology, Athens, Greece, [4]Nikaia, Greece, [5]Thriasio Hospital, Neurology, Elefsina, Greece, [6]Pammakaristos Hospital, Neurology, Athens, Greece, [7]Athens General Hospital "G. Gennimatas", Neurology, Athens, Greece, [8]Athens, Greece, [9]Panteion University, Psychology, Athens, Greece

Background and aims: Work engagement is defined as a positive, fulfilling, work-related state of mind that is characterized by vigor, dedication and absorption.

The purpose of our cross-sectional study was to investigate work engagement among neurology residents in the region of Attica,Greece, and identify factors associated with it,based on the job demands-resources model(JD-R).

Methods: In total, 131 placements for neurology training over 18 hospitals are available. All residents were approached and were asked to participate in the study by anonymously completing a questionnaire. Job demands were examined via a 17-item questionnaire assessing 4 characteristics (emotional demands, intellectual demands, workload, home-work demands' interface) and job resources were measured via a 14-item questionnaire assessing 4 characteristics (autonomy, opportunities for professional development, support from colleagues, supervisor's support). Work engagement was measured by the Utrecht Work Engagement Scale.

Results: 116 residents participated in the study (response rate 88.5%). Univariate analysis showed that work engagement was higher in females (47.4 versus 41.1, p=0.028). Moreover, work engagement correlated significantly with number of days off (Spearman's rho=0.207, p=0.027) home-work demands' interface (spearman's rho=-0.198, p=0.034), autonomy (rho=0.423, p<0.001), supervisor's support (rho=0.319, p=0.001) and opportunities for professional development (rho=0.610, p<0.001).

Conclusion: Work engagement during neurology residency is higher when opportunities for professional development are more,supervisor's support is present,autonomy is higher,days off are given and home-work demand's interface is less.Educators and program directors need to design interventions to promote residents' resilience and mental health.

Disclosure: Nothing to disclose

P2127

Neuroticism and job-related factors among neurology residents: results from the Attica Study

P. Zis[1], A. Artemiadis[2], M. Lykouri[1], S. Xirou[3], A. Roussopoulou[1], E. Papageorgiou[4], E. Bakola[5], P. Iliopoulos[6], I. Stavropoulos[7], S. Katsavos[8], F. Anagnostopoulos[9]

[1]Evangelismos General Hospital, Neurology, Athens, Greece, 2417 General Military Hospital Nimts, Neurology, Athens, Greece, [3]Eginition University Hospital, Neurology, Athens, Greece, [4]Nikaia, Greece, [5]Thriasio Hospital, Neurology, Elefsina, Greece, [6]Pammakaristos Hospital, Neurology, Athens, Greece, [7]Athens General Hospital "G. Gennimatas", Neurology, Athens, Greece, [8]Athens, Greece, [9]Panteion University, Psychology, Athens, Greece

Background and aims: Neuroticism is a fundamental personality trait characterized by emotional instability and negative affect. Individuals who score high on neuroticism are more likely than the average to exhibit anxiety, hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress. The purpose of our cross-sectional study was to investigate neuroticism among neurology residents in the region of Attica, Greece, and identify factors associated with it, based on the job demands-resources model (JD-R).

Methods: In total, 131 placements for neurology training over 18 hospitals are available. All residents were approached and were asked to participate in the study by anonymously completing a questionnaire. Job demands were examined via a 17-item questionnaire assessing 4 characteristics (emotional demands, intellectual demands, workload, home-work demands' interface) and job resources were measured via a 14-item questionnaire assessing 4 characteristics (autonomy, opportunities for professional development, support from colleagues, supervisor's support). Neuroticism was examined via a 12-item scale, based on the NEO-Five Factor Inventory.

Results: 116 residents participated in the study (response rate 88.5%). Univariate analysis showed that neuroticism correlated significantly with home-work demands' interface (Spearman's rho=0.384, p<0.001), emotional demands (rho=0.288, p=0.002), supervisor's support (rho=-0.272, p=0.004) and opportunities for professional development (rho=-0.256, p=0.006).

Conclusion: Neuroticism among neurology residents is associated with high emotional demands, high home-work demands' interface, poor supervisor's support and decreased opportunities for professional development. Educators and program directors need to design interventions to promote residents' resilience and mental health.

Disclosure: Nothing to disclose

P2128

Establish a specialist in neurology program in Brunei Darussalam with the help of telemedicine

U. Meyding-Lamadé[1], E.M. Craemer[1], B. Bassa[1], C. Chan[2], A. Masri[2], N. Yassin[2], Z. Hanafi[3], A. Aziz[3], W. Hacke[4]
[1]Krankenhaus Nordwest, Klinik für Neurologie, Frankfurt am Main, Germany, [2]Brunei Neuroscience Stroke and Rehabilitation Centre, Jerudong, Brunei Darussalam, [3]Universiti Brunei Darussalam, Jerudong, Brunei Darussalam, [4]Universitätsklinikum Heidelberg, Heidelberg, Germany

Background and aims: Neurology will be one of the major columns of medicine. A worldwide lack of neurological knowledge there is an obvious need for specialists in neurology. Since 7/2010 a transcontinental cooperation between the Brunei Neuroscience Stroke and Rehabilitation Centre(BNSRC), Brunei Darussalam(BD), the Department of Neurology, Krankenhaus Nordwest (KHNW), Frankfurt, Germany has been successfully implemented. BNSRC is the 1st neurological facility in BD, therefore local doctors has to be trained in neurology to ensure that they can handle the patients as well as to get a curriculum of neurology in order to become specialist in neurology. This program is established and conducted by Universiti Brunei Darussalam, University of Heidelberg, Germany, Johns Hopkins, USA, KHNW and BNSRC.

Methods: Total duration shall normally be at least 60 months full-time. We established a teleteaching program including on site teaching. Consisting of different modules; electrophysiology, EEG, clinical examination including scales for different diseases and the grand round. The grand round is basically a teaching ward round to discuss selected patients. Local doctors report the history, demonstrate physical symptoms,diagnostic work up and therapeutic strategies are discussed as well as all medical findings.

Results: 2 local doctors are enrolled, overall 7 doctors have taken part and passed all assessments.

Conclusion: Neurological diseases are a major column at present time and the prevention of neurological diseases are more important than ever. As there is a need of specialists in neurology worldwide, this specialist in neurology program can set a milestone in teaching of neurologic skills with the help of telemedicine to overcome distances.

Disclosure: Nothing to disclose

P2129

Setting up the Brunei Neuroscience Stroke and Rehabilitation Centre 12,000km away with the help of Telemedicine – To teach to treat – to treat to teach

U. Meyding-Lamadé[1], E.M. Craemer[2], C. Chan[3], N. Yassin[3], C. Jacobi[2], B. Bassa[2], A. Masri[3], I. Jafaar[4], Z. Hanafi[3], A. Aziz[5], B. Kress[6]
[1]Krankenhaus Nordwest, Klinik für Neurologie, Frankfurt am Main, Germany, [2]Krankenhaus Nordwest, Department of Neurology, Frankfurt am Main, Germany, [3]Brunei Neuroscience Stroke and Rehabilitation Centre, Jerudong, Brunei Darussalam, [4]Jerudong Park Medical Centre, Jerudong, Brunei Darussalam, [5]Universiti Brunei Darussalam, Jerudong, Brunei Darussalam, [6]Krankenhaus Nordwest, Department of Neuroradiology, Frankfurt am Main, Germany

Background and aims: Due to the worldwide aging population there is a need for specialist neurological knowledge. Our project in Brunei Darussalam (BD) offers to overcome distances and also a long-time benefit for patients. It comprises the set up of a local stroke unit, neurological intensive care unit, normal wards and neurorehabilitation. This has been achieved by continuous medical education and telemedical consultation

Methods: Set up of the Brunei Neuroscience Stroke and Rehabilitation Centre (BNSRC) started 7/2010. In order to overcome the distance,a telemedical network between the Department of Neurology of Krankenhaus Nordwest, Frankfurt, Germany (KHNW) and the BNSRC was established. This cooperation includes the development of a "specialist in neurology" training program, accredited in BD and an international advisory board. Daily teleteaching as well as 24/7 tele-neurology services are offered. All neurological laboratories have been set up on site, tele-cytology, tele-electrophysiology, EEG and ultrasound.

Results: Patients with stroke, intracerebral hemorrhages, aneurysms, encephalitis and other neurological diseases as in-and out and rehab patients have been seen. We evaluated 85% ischemic strokes and 15% hemorrhagic. Since 2010 27 thrombolysis, 24 hemicraniectomies, hypothermia, invasive intracranial pressure measurement have been also performed. We have achieved world class neurological intensive care standards in a short period. Training programs and the back up with telemedicine are ideal for teaching and treating in neurology.

Conclusion: Stroke is a major disease at the present time and prevention is more important than ever. Setting up BNSRC is not only a useful tool, for more it proved to be feasible and successful to cooperate irrespective of distance, religion and culture.

Disclosure: Nothing to disclose

P2130

Professionalism in the use of social networking sites: a survey among European residents and junior neurologists (RJN)

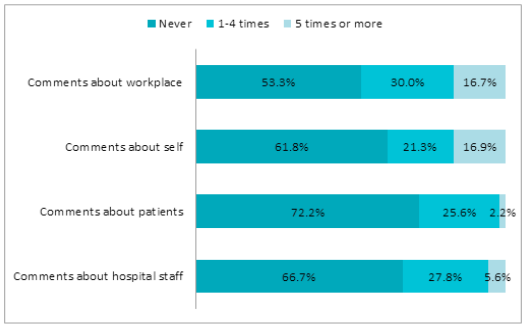
V. Papp[1], A. Macerollo[2], O. Györfi[3], P. Balicza[4], M. Moarcas[5], A. Sauerbier[6], P. Zis[7], L. Klingelhöfer[8], W. Struhal[9], J. Sellner[10]

[1]Holstebro Hospital, Holstebro, Denmark, [2]Aldo Moro University of Policlinico Hospital, Bari, Italy, [3]Nyírő Gyula Hospital, National Institute of Psychiatry and Addictions, Neurology, Budapest, Hungary, [4]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Neurology, Budapest, Hungary, [5]Emergency Clinical County Hospital Brasov, Neurology, Brasov, Romania, [6]King's college London and King's college hospital, Neurology, London, United Kingdom, [7]Evangelismos Hospital, Neurology, Athens, Greece, [8]Technical University Dresden, Neurology, Dresden, Germany, [9]Medical Faculty, Johannes Kepler University Linz, Neurology and Psychiatry, Linz, Austria, [10]Christian-Doppler-Klinik, Paracelsus Medical University, Neurology, Salzburg, Austria

Background and aims: Social networking sites (SNS) have increased exponentially in popularity and use. While SNS can yield opportunities for communication, education and patient care, it may be a platform for unprofessional behaviour. This study was to assess definition and personal experience with professionalism for the use of SNS among European residents and junior neurologists (RJN).

Methods: A paper questionnaire was distributed to RJN during the ENS-EFNS congress (Istanbul, June 2014) at the booth of the EAYNT.

Results: 92 RJN (66.3 % female) from 20 different countries returned the survey. The majority (85.9%) uses Facebook (FB), 52.2% have Twitter accounts. FB mostly has a status as platform to keep in touch with friends (72.2%). 35.4% strongly disagree with accepting friend requests from patients, and to post patient information (69.6%) and work-related issues (40.5%). Some RJN assume that their posts can influence patients (36.7 %) and future employment (26.5 %). A minority (11.6%) states that it is completely appropriate to access SNS at work. Figure 1 summarises domains of inappropriate postings during the last 12 months. This concerned the workplace (46.7%), self (38.2%), hospital staff (33.4%) and patients (27.8%).



Inappropriate social network posting during the last 12 months

Conclusion: The usage of SNS is common among RJS and inappropriate behaviour is frequently encountered. We demonstrate a considerable diversity of perception for professionalism and inadequate translation into daily practice. RJN need to be aware of institutional policies defining appropriate online behaviour and post-graduate curricula may take education for principles of online professionalism into account.

Disclosure: Nothing to disclose

P2131

Abstract cancelled

Epilepsy 1

P2132

Estimation of the direct cost of epilepsy among Sudanese patients attending charity clinic in Omdurman 2014

M.A. Abdelrahim[1], M.M. Alfaki[1], R.A. Alsherif[1], M.D. Dafaalla[1], M.I. Alfaki[1], M.A. Taha[1], A.S. Ahmed[1], M.S. Abd Elmotalib[1], M.A. Alnor[1], D.N. Osman[1], A.M. Hussein[2]

[1]Daoud Research Group, Khartoum, Sudan, [2]Faculty of medicine, University of Khartoum, Department of Neurology, Khartoum, Sudan

Background and aims: The economic burden of epilepsy in the developing countries didn't receive enough attention. We have estimated the direct and some of the indirect costs of epilepsy among patients attending charity clinic in Sudan.

Methods: The study was performed on a case series of medically treated Sudanese patients with epilepsy in a charity clinic. Data on clinical characteristics, utilization of medical services, and costs were collected from 38 patients in a standardized pre-tested format.

Results: Direct medical care costs was Sudanese Pounds (SDG) 2,395 (USD 417) per year per patient, of which antiepileptic drugs SDG 1,587 (USD 276) accounted for the major cost component. Direct cost also included medical consultations and hospitalization charges SDG 148 (USD 26), investigation costs SDG 146 (USD 25), and cost of travel to clinics SDG 514 (USD 90). Nonmedical direct costs - in form of traditional healers' visits - were reported by 13.5% of the patients and estimated to be SDG 1,422 (USD 251). The indirect cost was estimated for co-patients transportation (reported by 7.9% of the patients who are resident outside the state) estimated to be SDG 1,773 (USD 308) per co-patient per year. Taken together, the overall mean annual cost for epilepsy per patient in our clinic was approximately SDG 2,724 (USD 474).

Conclusion: The results indicate that the economic burden of epilepsy patients is heavy, and the composition proportions of the costs in Sudan have many similar features and some noteworthy differences with that of other countries.

Disclosure: Nothing to disclose

P2133

The association of medications adherence with the quality of life and the costs of epilepsy among Sudanese epilepsy patients attending charity clinic in Omdurman

M.A. Abdelrahim[1], M.D. Dafaalla[1], M.M. Alfaki[1], R.A. Alsherif[1], M.I. Alfaki[1], M.A. Taha[1], A.S. Ahmed[1], M.S. Abd Elmotalib[1], M.A. Alnor[1], D.N. Osman[1], A.M. Hussein[2]

[1]Daoud Research Group, Khartoum, Sudan, [2]Faculty of medicine, University of Khartoum, Department of Neurology, Khartoum, Sudan

Background and aims: To assess the association of medications adherence with the quality of life and the costs of epilepsy in a sample of Sudanese patients with epilepsy.

Methods: The study was performed on Daoud charity neurological clinic epilepsy patients from June to September 2014. Data on clinical characteristics, utilization of medical services, and costs were collected. Medication adherence was assessed using Morisky Medication Adherence Scale (MMAS-8). Quality of life was assessed using WHO Quality of Life Brief-26.

Results: There were 38 patients (71% males; mean age 32.9 years). According to MMAS-8, (23.7%) of patients had a high adherence, (39.5%) had a medium adherence and (36.8%) had a low adherence rate. The mean total score of WHOQOL Brief was (91.8 out of 130). The overall mean annual costs were 2,778 Sudanese Pounds (USD, 484). Adherence score was positively and significantly correlated with WHOQOL Brief total score (P=0.008), Physical Health domain score (P=0.007), Social relationships domain score (P=0.006), and environment domain score (P=0.007). Similar significant correlation was found between the overall mean annual costs and the environment domain score (P=0.041). However, adherence was not associated with psychological domain score (P=0.054), the annual total costs of epilepsy (P=0.568) or the annual medications costs of epilepsy (P=0.87).

Conclusion: We conclude that participants with low quality of life are more likely to have lower adherence to antiepileptic medications. In spite of the high annual costs of epilepsy, it does not affect patients' adherence to medications. The psychological aspect of the quality of life of epilepsy patients does not affect their medications adherence.

Disclosure: Nothing to disclose

P2134

Status epilepticus in the elderly

K. Agan Yildrim[1], I. Midi[2], C. Aykut-Bingol[3]
[1]Istanbul, Turkey, [2]Marmara University, Neurology, Istanbul, Turkey, [3]Yeditepe University Hospital, Neurology, Istanbul, Turkey

Background and aims: The aim of this study was to evaluate the risk and prognostic factors and outcome of status epilepticus (SE) among elderly patients. We investigated clinical and demographic characteristics of patients over 60 years of age who presented with SE.

Methods: Between 1998 and 2009, 165 (44 male, 121 female) consecutive patients over 60 years of age were included. We assessed etiology and type of treatment as a prognostic factor to determine outcome.

Results: Median age was 73.8 (range 61-93). Nonconvulsive Status Epilepticus (NCSE) including Convulsive Status Epilepticus (CSE) turned to NCSE was the most frequent type (72.7%). An acute cerebrovascular disease (22.2%) was the most common etiology followed by acute metabolic disturbances (17.6%) and remote symptomatic (cerebrovascular disease 15.8%, brain tumors 9.1%). Only 20.9% of the patients had a history of epilepsy before SE. 41.1% of the patients evolve in to refractory SE (RSE).

Conclusion: Status Epilepticus without a history of epilepsy is common among elderly. Cerebrovascular disease either acute or remote symptomatic are amongst the most common causes. NCSE is the most common type of SE in elderly.

Disclosure: Nothing to disclose

P2135

Effects of lamotrigine on bone mineral density

D. Aksoy[1], D. Ataklı[2]
[1]Nicosia state hospital, neurology, Nicosia, Cyprus, [2]Bakirköy psNeurological and Psychiatric Disease Teaching and Research Hospital , neurology, Istanbul, Turkey

Background and aims: The objective of this study was to examine the effects of lamotrigine (LTG) monotherapy on bone mineral density in epilepsy patients taking LTG.

Methods: In this cross-sectional study we analized data from 20 healthy women and 18 female idiopathic generalised epilepsy patients who have been monitored in Bakirkoy Neurological and Psychiatric Disease Teaching and Research Hospital Epilepsy Policlinic. Clinical and demographical properties of the patients were reviewed. Serum calcium, ionized calcium and vitamin D levels of the two groups were evaluated.

Results: The mean age of the epilepsy patients and the control group were 27.00±10.27 and 28.95±4.21 respectively. The mean disease period was 7.8±9.5 years (1-42). LTG treatment period was evaluated as 6.61±2.9 years (2-11). The mean dosage of LTG was 123.6±55.8mg/day (50-225). No significant differences were observed in calcium and ionized calcium levels between patient and the control group ($p>0.05$). On the other hand, vitamin D levels were lower in the patient group which was statistically significant ($p=0.03$). The duration of LTG use or daily LTG dosage had no correlation with the calcium, ionized calcium and vitamin D levels ($p>0.05$).

Conclusion: Serum calcium and ionized calicium levels were found normal in patients receiving LTG monotherapy. However, Vitamin D concentrations were lower in patients than in control subjects. We suggest that calcium and vitamin D levels in patients receiving LTG should be monitored closely. In addition, regular diet, physical exercise and exposing their bare skin to sunlight should be recommended.

Disclosure: Nothing to disclose

P2136

Mutation in the KCNQ2 gene – a rare cause for Rolandic epilepsy

I. Aleksandrova[1], V. Bojinova-Tchamova[1], N. Ivanova[2], E. Slavkova[1], P. Dimova[3], V. Pejcheva[2], K. Kamenarova[2], R. Kuneva[2], A. Jordanova[2]

[1]Clinic of Child Neurology, University Hospital for Active Treatment of Neurology and Psychiatry "St. Naum", Sofia, Bulgaria, [2]Molecular Medicine Center, Medical University of Sofia, Sofia, Bulgaria, [3]Epilepsy Surgery Center, Department of Neurosurgery, Multiprofile Hospital for Active Treatment "St. Ivan Rilski", Sofia, Bulgaria

Background and aims: Benign epilepsy with centrotemporal spikes (BECTS) is the most common epilepsy syndrome in childhood. Diagnosis is based on typical clinical features and EEG. The prognosis is favorable with a complete remission until puberty. The genetic factor in BECTS etiology is very interesting and a number of responsible genes have been defined. KCNQ2 mutations were initially described in benign familial neonatal seizures (BFNS), which, like in rolandic epilepsy, are age-related and with a favorable outcome. However, severe KCNQ2-related epileptic encephalopathy has recently been reported. Familial cases of KCNQ2-related BFNS have also been described with a subsequent manifestation of rolandic epilepsy. In these cases, the role of the mutation for the earlier onset of BECTS is discussed.

Methods: We present the case of a boy who experienced generalized tonic-clonic seizures (GTCS) when 4 months old and seizures after falling asleep at the age of 3 years, which, based on the clinical and EEG features, were discussed as Rolandic seizures. The family history of the patient revealed that his brother had seizures that started when he was 5 days old and his father experienced seizures during infancy. These attacks, including the earlier GTCS of the patient, were discussed as BFNS and benign familial infantile seizures (BFIS) with post-BFIS development of BECTS in the proband.

Results: The genetic analysis showed mutation c.1174G>A (p.R333Q) of the KCNQ2 gene.

Conclusion: In such cases, the genetic analysis will allow genetic counseling for subsequent pregnancies and will facilitate the diagnosis and therapy of seizures occurring in other family members.

Disclosure: Nothing to disclose

P2137

Ictal asystole requiring pacemaker implantation: combined EEG / ECG study of 5 cases

R. Bartlam[1], R. Mohanraj[2]

[1]University of Manchester, Manchester Medical School, Manchester, United Kingdom, [2]Salford, United Kingdom

Background and aims: Seizures can lead to cardiac arrhythmias by a number of mechanisms including activation/inhibition of cortical autonomic centres, increase in vagal tone through activation of brainstem reflex centres and as a consequence of respiratory failure. Ictal asystole (IA) is a potential mechanism underlying Sudden Unexpected Death in Epilepsy (SUDEP). We analysed the clinical features of 5 patients who developed IA requiring pacemaker implantation

Methods: Patients with ictal arrhythmias identified from the video-telemetry and ambulatory EEG database at Greater Manchester Neurosciences Centre, as well as an independent epilepsy residential care facility. Only those who had IA requiring pacemaker implantation were included in the analysis. A total of 5 patients were identified

Results: Of the 5 patients with IA, 4 were female. All 5 patients had focal epilepsy, and four had temporal lobe epilepsy. IA occurred with complex partial seizures, 2-45 seconds (mean 25 seconds) after EEG seizure onset in all cases. Seizure onset was left sided in 2 patients, right sided in one, left sided onset with switch of lateralisation in one, and non-lateralised in 1 patient. 2 patients had traumatic encephalomalacia of the temporal lobe, and 1 patient had hippocampal sclerosis and 2 patients had no lesions detected on MRI. Inter-ictal epileptiform activity was more pronounced during sleep in four patients. Asystole occurred following sleep related seizures in 3 of 5 patients.

Conclusion: IA was most frequently observed in patients with temporal lobe epilepsy, and in sleep related seizures. These findings maybe of relevance to SUDEP.

Disclosure: Nothing to disclose

P2138

Hippocampal subfield volumes in physiological déjà vu versus mesial temporal lobe epilepsy and schizophrenia

M. Brázdil
Brno, Czech Republic

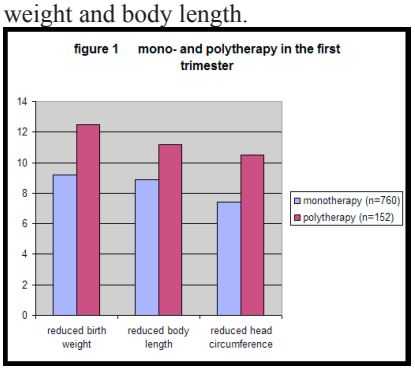
Background and aims: A significantly less gray matter was recently revealed within a set of cortical (predominantly both-sided hippocampi) and subcortical regions in healthy subjects experiencing déjà vu (DV) when compared to déjà vu non-declarers. Despite observed GM volume differences mirrored the distribution of GM volume reduction in subjects suffering from mesial temporal lobe epilepsy (MTLE), the pattern of GM differences within hippocampi were distinctive between MTLE and DV. Schizophrenia (SCH) represents another condition in which hippocampal GM volume was found to be significantly decreased .
Methods: In this study we compared differences in GM volume within distinctive hippocampal subfields among healthy DV non-declarers (N=26) and healthy DV declarers (N=85), MTLE (N=47) and schizophrenia (N=46) patients alternatively. The images were automatically segmented and registered using SPM8 and its toolbox DARTEL. Local GM volume was corrected with respect to age, gender and total intracranial volume. The decrease of local GM volume across voxels (relatively to the nonDV group) was correlated between DV and MTLE and between DV and SCH.
Results: The results revealed significant correlations between GM volume reduction in DV and SCH as well as DV versus MTLE in the majority of analyzed hippocampal subfields. Importantly GM volume correlations were significantly higher for SCH (than MTLE) within left CA4+DG, left and right CA2+3, and left presubiculum. The only significantly higher correlation for MTLE was observed within right subiculum.
Conclusion: Our findings reveal common structural features of hippocampal involvement in physiological déjà and both investigated SCH and MTLE.
Disclosure: Nothing to disclose

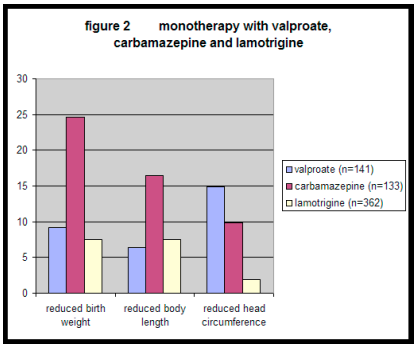
P2139

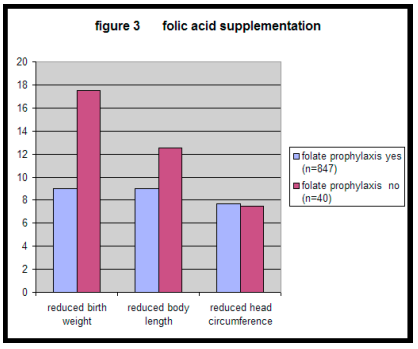
An update on data from German Registry of Antiepileptic Drugs and Pregnancy (GRAP): risks of growth delay

H. Cakiroglu, M. Bengner, S. Nazari Dehkordi, B. Schmitz
Berlin, Germany

Background and aims: GRAP is an observational study to investigate pregnancies with antiepileptic drug (AED) exposition. Women who take AEDs at the time of conception are included and observed until 1 year post partum. We aimed to establish the influence of the prenatal exposure to AED and folate prophylaxis on fetal growth.
Methods: Until January 2015, 1078 pregnancies had been registered in GRAP. 940 of the women have given birth so far. The frequency of delayed growth referred to birth weight, body length and head circumference were analysed. Measurements under the 10th percentile were classified as growth delay.
Results: 80.9% of the women were treated in AED monotherapy and 16.2% in polytherapy. 9.5% of the infants had based on their gestational age a low birth weight <10th percentile. Growth delay was more frequently observed in association with AED poly- compared to monotherapy. The three AEDs most frequently prescribed were lamotrigine (=362), valproate (n=141), and carbamazepine (n=133). In the three groups of AED monotherapy the rate for reduced birth weight (24.6%) and body length (16.5%) was highest for carbamazepine. 90.1% of the GRAP-women took folic acid. Among mothers without folate prophylaxis (n=40) there was a larger proportion of infants with reduced birth weight and body length.







Conclusion: Prenatal polytherapy with AEDs and nonexisting folic acid supplementation seem to be potential risk factors for delayed fetal growth. Considering the low sample sizes and missing confounding factors the statistical significance will probably be clarified in future investigations.
Disclosure: Nothing to disclose

Motor neurone diseases 2

P2140

Genome-wide changes in TDP43-dependent splicing caused by endogenous mutations are insufficient to cause neuronal degeneration in the laboratory mouse

H. Oliveira[1], T. Ricketts[2], P. Fratta[3], E. Fisher[3], V. Plagnol[3], A. Acevedo-Arozena[4]
[1]*MRC Harwell/University of Oxford, Oxford, United Kingdom,* [2]*MRC Harwell, Neurodegeneration Group, Oxfordshire, United Kingdom,* [3]*University College London, London, United Kingdom,* [4]*MRC Harwell, Oxfordshire, United Kingdom*

Background and aims: TDP43 is a highly conserved, ubiquitously expressed protein with multiple roles in RNA metabolism, including alternative exon splicing, which plays a pivotal role in neurodegeneration. Abnormally aggregated cytoplasmic TDP43, which is cleaved, hyperphosphorylated and polyubiquitinated is a histopathological hallmark of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and mutations in TARDBP (the gene encoding TDP43) are causative of ALS and FTD. Transgenic animal models engineered to over-express, knockdown or conditionally delete TDP43 have all been shown to develop neurodegeneration. Furthermore, dysregulation in TDP43-dependent alternative exon splicing has been reported in many of these models, and thus hypothesised to lead to neurotoxicity.

Methods or Materials or Case Report: Using a reverse genetics approach we have characterised two ENU Tardbp mouse mutants with mutations in the second RNA Recognition Domain (Phelynalanine to Isoleucine at amino acid residue 210) and in the Glycine-rich C-terminal (Methionine to Lysine at amino acid residue 323) of TDP43.

Extensive molecular and behavioural characterisation was performed longitudinally on heterozygous animals for both mutations.

Results: The results revealed that the F210I and M323K mutations have opposite effects in TDP43-dependent splicing, with the former leading to a dose-dependent "loss of normal function" and the latter the opposite effect, at the genome wide level. Metabolic effects were seen in Tardbp-F210I/+ females which displayed lower body weight throughout most its lives.

Nevertheless, neither TardbpF210I/+ or Tardbp323K/+ developed neurodegeneration.

Conclusion: Our results show, for the first time, that dysregulation in TDP43-dependent splicing at the genome wide level is insufficient to cause neuronal toxicity in the mouse during its normal lifespan.

Disclosure: The research presented in this abstract has received generous funding from the Medical Research Council, Motor Neurone Disease Association, Genetics Society and Disease and Model Mechanisms.

P2141

Immunohistochemical studies of FUS in the skin in sporadic amyotrophic lateral sclerosis

S. Ono
Ichihara, Japan

Background and aims: Several studies of skin in patients with sporadic amyotrophic lateral sclerosis (SALS) have shown unique morphological and biochemical alterations. The lack of bedsore formation even in the terminal stages in ALS patients is considered characteristic. Recently, mutations in a gene coding the fused in sarcoma (FUS) have been identified in familial amyotrophic lateral sclerosis (ALS). Also, FUS has been found in neuronal cytoplasmic inclusions in sporadic ALS, suggesting that FUS has an important role in the neurodegeneration occurring in ALS, However, there has been no study of FUS in ALS skin.

Methods: We have performed a quantitative immunoreactive study of FUS in biopsied skins from 22 patients with sporadic ALS and from 22 controls. Routine formalin-fixed paraffin-embedded 6 μm sections were immunostained according to standard techniques. A densitometric analysis was performed using an image analysis system.

Results: The proportion of FUS-immunoreactive (ir) cells in the epidermis in ALS patients was significantly higher ($p<0.001$) than in controls. There was a significant positive relationship ($r=0.78$, $p<0.001$) between the proportion and duration of illness in ALS patients. The optical density of FUS-ir cells in the epidermis in ALS patients is markedly stronger ($p<0.001$) than in controls. There was a significant positive relation ($r=0.49$, $p<0.05$) between the immunoreactivity and duration of illness in ALS patients.

Conclusion: These data suggest that changes of FUS in ALS skin are related to the disease process and that metabolic alterations of FUS may take place in the skin of patients with ALS.

Disclosure: Nothing to disclose

P2142

Radiotherapy (RT) of salivary glands as treatment of sialorrhea in patients with amyotrophic lateral sclerosis (ALS) requiring non-invasive ventilation (NIV)

A. Assouline[1], J. Gonzalez-Bermejo[2], P.-F. Pradat[3], M.D.M. Amador[4]

[1]Centre Clinique de la Porte de Saint-Cloud, Radiotherapy, Boulogne-Billancourt, France, [2]Pitié-Salpêtrière University Hospital, Pneumology, Paris, France, [3]Pitié-Salpêtrière University Hospital, Neurology, Paris, France, [4]Hôpital Pitié Salpétrière, Département des maladies du Système Nerveux Central, UF Neurométabolique, Paris, France

Background and aims: Sialorrhea in ALS patients is a frequent and disabling problem that also limits efficiency and tolerance of non invasive ventilation (NIV). We recently demonstrated in a large series of ALS patients that radiotherapy (RT) of the salivary glands is both efficient and safe. Performing this method in patients requiring NIV during decubitus is technically challenging since it needs to adapt the method of RT.

Methods: A thermoplastic mask for RT was specifically designed to fit the NIV interface (figure 1). 5 ALS patients treated with NIV suffering from severe sialorrhea were treated with RT using this new mask. Treatment was delivered through a linear accelerator with 6 MV photons including both submandibular and parotid glands. Total RT dose was 10 Grays/2 fractions. RT efficacy was assessed with a 9-grades Sialorrhea Scoring Scale (SSS).

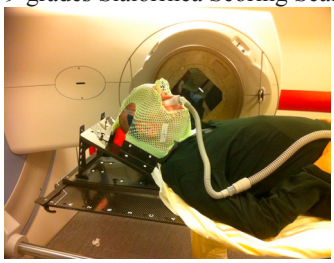


Figure 1

Results: At the end of RT, all patients had improved: 4 had a complete response (80% CR: SSS 1-3) and 1 had a partial response (20% PR: SSS 4-5). A significant lasting salivary reduction was observed 3 months after RT completion: there was 60% CR and 40% PR. Acute toxicity was observed in 2 patients (mild pain and saliva thickening). There was no grade 3-4 toxicity. All side effects resolved in the weeks following the end of treatment.

Conclusion: Radiotherapy method can be adapted for treating sialorrhea in ALS patients requiring NIV. This treatment is both efficient and safe. Larger prospective studies remain needed to confirm these results and specify its potential impact on NIV efficacy and tolerance and survival.

Disclosure: Nothing to disclose

P2143

The wide clinical phenotype of Kennedy's disease.

G. Querin[1], E. da Re[2], C. Bertolin[2], M. Volpe[1], N. Caretta[1], C. Foresta[1], M. Iafrate[1], D. Corrado[1], M. Silvano[1], E. Pegoraro[1], D. Pareyson[3], M. Pennuto[4], G. Sorarù[2]

[1]Università degli Studi di Padova, Padua, Italy, [2]Università di Padova, Neuroscienze, Padua, Italy, [3]Istituto Neurologico C. Besta, Milan, Italy, [4]Università di Trento, Trent, Italy

Background and aims: KD is a neuromuscular disease caused by a CAG repeat expansion in the androgen receptor (AR) gene. AR is broadly expressed in the body, thus AR toxicity may involve organs other than the neuromuscular system. The aim of this study was to describe the clinical phenotype in a large population of Kennedy's disease (KD) patients.

Methods: A clinical protocol focused on androgen-linked functions was administered to 72 Caucasian KD patients. It included: neurological exam, blood tests (glucose and lipid metabolism, hormonal status, bone metabolism), bone density test, and EKG. Urinary and sexual functions were also assessed by the means of functional scores and prostate echography.

Results: Mean age at onset was 46 years and lower limb weakness was reported as presenting symptom in most cases. Patients presented a tendency to overweight with sugar levels consistent with diabetes mellitus or with impaired glucose tolerance in almost 50% of cases. 38% of patients had borderline blood total cholesterol levels, while 15% had an overt hyperlipidemia. Hormonal assessment was unremarkable. Bone density test showed femoral osteopenia in 45% of patients regardless of their age. No significant heart rhythm disorders were recorded. One third (37%) of patients complained urinary symptoms, which scored moderate to severe according to the functional scales and were unrelated to prostate hypertrophy. Erectile dysfunction was reported in 46% of cases.

Conclusion: This study further widens the clinical spectrum of KD.

Disclosure: Nothing to disclose

P2144

Effects of cough augmentation on pulmonary morbidity, survival, and quality of life in patients with amyotrophic lateral sclerosis in respiratory failure: a randomised trial

M. Rafiq[1], M. Bradburn[2], C. McDermott[1], P. Shaw[1]
[1]University of Sheffield, Neuroscience, Sheffield, United Kingdom, [2]University of Sheffield, Clinical Trials Unit, Sheffield, United Kingdom

Background and aims: A major problem faced by patients with amyotrophic lateral sclerosis (ALS) in respiratory failure is inability to cough effectively and remove secretions from the airways.

Methods: A total of 40 eligible ALS patients were randomised to breath-stacking technique (n=21) or mechanical insufflator/exsufflator MI-E (n=19) and followed-up at 3 monthly intervals for at least 12 months or until death.

Results: There were 13 episodes of chest infection in the breath-stacking group and 19 episodes in MI-E group (p=0.87), requiring 90 and 95 days of antibiotics respectively (p=0.85). There were 6 episodes of hospitalisation in each group (p=0.87). The mean duration of symptoms per chest infection was 6.9 days in the breath-stacking group and 3.9 days in MI-E group (p=0.16). Chance of hospitalisation, in the event of a chest infection was 0.46 in the breath-stacking group and 0.31 in MI-E group (p=0.47). Median survival in the breath-stacking group was 535 days and 266 days in the MI-E group (p=0.34). Quality of life was maintained above 75% of baseline for a median of 329 days in the breath-stacking group and 205 days in MI-E group (p=0.41).

Conclusion: In ALS patients with respiratory failure, cough augmentation is likely to improve survival while maintaining quality of life. The breath-stacking technique may be prescribed for domiciliary use with the onset of respiratory failure. MI-E may be useful in the event of a chest infection when it is likely to reduce the duration of antibiotic use and chance of hospitalisation.

Disclosure: Nothing to disclose

P2145

Cerebral motor cortex at 7T MRI and clinical correlates in amyotrophic lateral sclerosis

G. Siciliano[1], G. Donatelli[2], I. Pesaresi[2], M. Costagli[3], E. Caldarazzo Ienco[1], M. Fabbrini[1], M. Rossi[1], L. Biagi[4], M. Tosetti[4], M. Cosottini[5]
[1]Department of Clinical and Experimental Medicine, Neurological Clinic, University of Pisa, Pisa, Italy, [2]Neuroradiology Unit, Department of Diagnostic and Interventional Radiology, Azienda Ospedaliero-Universitaria Pisana (AOUP), Pisa, Italy, [3]IMAGO[7] Foundation, Pisa, Italy, [4]Stella Maris Scientific Institute, Pisa, Italy, [5]Neuroradiology Unit, Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy

Background and aims: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by a progressive upper and lower motor neurons degeneration. Previous studies reported thinning and hypointensity of motor cortex in ALS. We aim to investigate by 7T images the morphology of deeper layers of motor cortex in ALS patients and correlate these data with clinical parameters.

Methods and Materials: 13 ALS patients and 13 age-matched healthy subjects (HS) underwent a 7T-MR examination; a high-resolution GRE sequence targeted on motor cortex was performed. Subjects were subjectively diagnosed on the basis of morphologic criteria, moreover thickness and signal intensity of deeper motor cortex were measured. Morphologic parameters were correlated with upper motor neuron burden (UMN-score), ALS-FRSr score and disease progression rate (DPR); patients were divided in "faster" and "slower" DPR.

Results: Sensitivity, specificity, PPV, NPV and diagnostic accuracy in distinguishing between patients and HS were low (69%, 77%, 75%, 71%, 73%) but UMN-score was significantly higher in true-positives than in false-negative (p=0.002). Cortical thickness was lower in patients than in HS (p=0.002) and correlated with UMN-score (R=0.63). Signal intensity was lower in "faster" than in "slower" DPR (p-value= 0.004) and correlated with UMN-score (R=0.65), ALS-FRSr (R=0.62) and DPR (R=0.71).

Conclusion: High resolution imaging at 7T allows the study of the fine structure of the cerebral motor cortex and may play a role as an early biomarker of UMN involvement in ALS patients. Further studies are necessary to confirm a role of UHF-MR imaging in monitoring the progression rate.

Disclosure: Nothing to disclose

P2146

Amyotrophic lateral sclerosis and schizophrenia in a family with C9orf72 hexanucleotid expansion

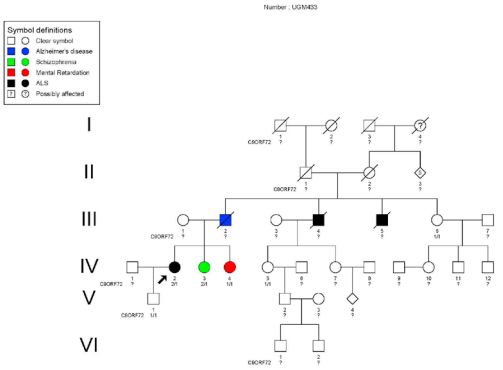
J.F. Vázquez Costa[1], J. Pérez Tur[2], A. Sabater Ferragut[3], P. Sopena Novales[4], M. Frasquet Carrera[5], M.T. Sevilla Mantecon[1]

[1]Hospital la Fe, Neurology, Valencia, Spain, [2]IBV-CSIC, Molecular genetics, Valencia, Spain, [3]Hospital la Fe, Psychiatry, Valencia, Spain, [4]Hospital la Fe, Radiology, Valencia, Spain, [5]Valencia, Spain

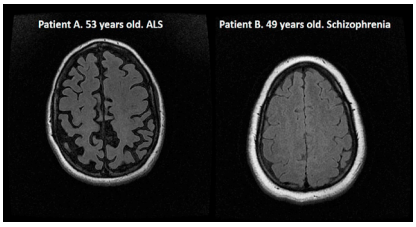
Background and aims: An hexanucleotid expansion in C9orf72 is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and Frontotemporal Dementia with TDP43 (FTD-TDP43). Recently, an aggregation of certain psychiatric diseases (schizophrenia and suicide) in relatives of C9orf72 positive ALS patients has been found. However, no family with ALS and schizophrenia patients carrying the C9orf72 expansion has been described.

Case Report: We describe two siblings, carrying a C9orf72 expansion, diagnosed with ALS and schizophrenia.

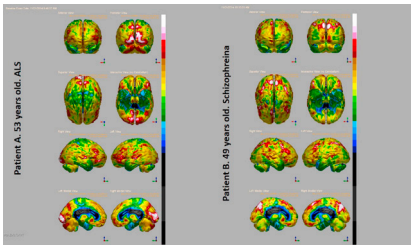
Results: A 53-year-old woman with family history of ALS and Alzheimer's disease, was evaluated after 1 year history of progressive weakness and atrophy in left hand. On examination, mild weakness and atrophy with hyperreflexia as well as an impairment of memory, language and executive functions were found. EMG confirmed the involvement of two regions; MRI and PET showed widespread (mainly parietal) brain atrophy and hypometabolism. She was diagnosed with probable ALS according to the El Escorial criteria and tested positive for C9orf72 expansion. After familial screening, her younger sister, a 49-year-old woman diagnosed with paranoid schizophrenia 30 years before, was also carrying the expansion. Her neurological examination was unremarkable but her memory and visuospatial functions were impaired. MRI did not show atrophy and PET showed mild hypometabolism in frontotemporo-occipital cortex.



Pedigree



MRI



PET

Conclusion: We comprehensively describe for the first time clinical and neuroimaging characteristics of two C9orf72 positive siblings diagnosed with ALS and schizophrenia. Our findings further reinforce the link between ALS and schizophrenia and suggest that different mechanisms (neurodevelopmental vs neurodegenerative) could lead to diverse clinical pictures in C9orf72 carriers.

Disclosure: This research work was supported with a grant of the Research Institute of La Fe Hospital (IIS La Fe)

Movement disorders 5

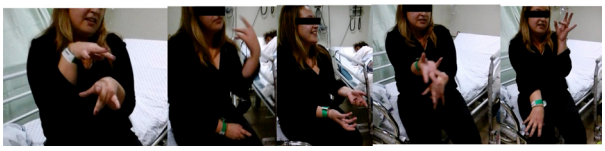
P2147

Psychogenic tics with incongruent gait as a give away

R. Araújo, J. Ribeiro, S. Batista
CHUC, Neurology, Coimbra, Portugal

Background and aims: Psychogenic tics are amongst the rarest of functional movement disorders. Incongruity is key in the correct diagnosis of these particularly challenging patients. Incongruity of gait disorder has recently been pointed out as a useful clue in diagnosing functional movement disorders (Balint et al, 2014).

Case Report: A 32-year-old woman, with a previous history of anxiety but no history of tics or Tourette's Syndrome, presented with acute-onset motor tics. The tics were complex, involved both arms and hands, and consisted of quick movements of the arms with dystonic posturing of the fingers, predominantly the second and fifth. Her relaxed demeanor suggested belle indifference. The movements were largely beyond the patient's control, but were suppressible to a certain degree. The disorder began abruptly after an altercation with the patient's father. On gait evaluation, the patient displayed incongruity with the presenting movement disorder or with any type of organic gait disorder, with myoclonus, chorea and astasia-abasia with a narrow base.



Tics while sitting, bilateral, with dystonic posturing. Belle indifference is also present.

Gait with prominent astasia-abasia, narrow base and chorea like movements (while wearing heels).

Gait also displayed myoclonic-like jerks of the inferior limbs and significant sway, always with a narrow base.

Results: The symptoms disappeared after diazepam 5 per os.

Conclusion: Gait is a solid give-away for diagnosing a functional movement disorder. Adult-onset tics are rare and could have prompted investigation for a secondary cause. The incongruity of the gait disorder and the patient's response to a benzodiazepine prevented unnecessary and potentially harmful further testing.

Disclosure: Nothing to disclose

P2148

The impact of white matter damage on cognition in PSP syndrome: a DT MRI study

F. Caso[1], F. Agosta[1], M.A. Volonté[2], A. Marcone[3], M. Copetti[4], F. Spagnolo[2], M. Falautano[2], A. Falini[5], G. Comi[2], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neuroscience, Milan, Italy, [4]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [5]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To explore the impact of white matter (WM) tract damage on cognitive performances in a relatively large sample of patients with probable progressive supranuclear palsy syndrome (PSPs) using diffusion tensor (DT) MRI.

Methods: We enrolled 32 patients with probable PSPs in a moderate stage of the disease (mean H&Y score: 3.3) and 22 matched healthy controls. Patients underwent an extensive neuropsychological evaluation. DT MRI and tract-based spatial statistics were used to assess the regional patterns of WM microstructural damage in patients relative to controls. Then, a regression analysis was conducted to correlate DT MRI metrics of the main WM tracts with cognitive variables.

Results: PSPs patients showed prominent attentive-executive deficits that were related to the damage of specific WM tracts as revealed by DT MRI. The following significant correlations were observed: attentive matrices scores with WM damage of the fornix, left cingulum, superior longitudinal fasciculus (SLF), right superior fronto-occipital fasciculus and bilateral cortico-spinal tract (CST); Raven matrices scores with fornix; token test scores with DT MRI measures of the fornix, bilateral inferior and middle cerebellar peduncle, cingulum, CST, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, left SLF and splenium of corpus callosum; fluencies scores with damage to bilateral superior cerebellar peduncles, left SLF and CST.

Conclusion: In PSPs, WM damage has a central role in the development of executive and language dysfunction.

Disclosure: CurePSP Foundation (#MD505-12_001).

P2149

Favourable effect of safinamide on dyskinesia evolution over 2-year treatment of fluctuating Parkinson's disease patients

C. Cattaneo[1], E. Bonizzoni[2], R. La Ferla[3], M. Sardina[3]

[1]Bresso (Milan), Italy, [2]University of Milan, Department of Clinical Science and Community, Section of Medical Statistics and Biometry "G.A. Maccacaro", Milan, Italy, [3]Zambon SpA, Medical Department, Bresso (Milan), Italy

Background and aims: Safinamide (Xadago™, Zambon SpA, Italy), a new drug with a dual mechanism of action, has shown in study 018 to reduce, after 24 months of treatment, the Dyskinesia Rating Scale (DRS) scores up to 31% from baseline, compared to 3% with placebo. The objective of this post-hoc analysis it to investigate the long-term effect of safinamide vs. placebo on dyskinesia as add-on therapy in fluctuating Parkinson's disease patients, treated with levodopa alone or in combination with dopamine agonists and/or anticholinergics.

Methods: The categorical changes in DRS scores were evaluated by stratifying the patients based on the presence or absence of dyskinesia at baseline and of changes in L-dopa doses.

Results: Safinamide 100 mg/day significantly improved the DRS score over 2 years of treatment, compared with placebo, both in patients with dyskinesia at baseline ($p=0.0153$) and in the overall population ($p=0.0488$). A borderline statistically significant improvement was also seen in patients with no changes in L-dopa dose ($p=0.0546$).These findings confirmed the results of a previous post-hoc analysis in patients with moderate to severe dyskinesia at baseline (DRS >4) showing a statistically significant decrease in DRS scores vs placebo at the dose of 100 mg ($p=0.0317$).

Conclusion: Patients treated with safinamide showed a significant improvement of dyskinesia in the long-term, as measured by DRS scores, apparently not related to L-Dopa dose changes. This may be explained by the safinamide non-dopaminergic mechanism of action, causing an inhibitory effect on glutamate release.

Disclosure: Carlo Cattaneo, Roberto La Ferla and Marco Sardina are employees of Zambon Pharma SpA. Erminio Bonizzoni is a consultant for statistical analyses of Zambon SpA.

P2150

Abstract cancelled

P2151

Effect of Catecho-O-metyltransferase (COMT) genotype on the response to bilateral subthalamic deep brain stimulation (DBS-STN) in Parkinson's disease (PD)

F. Cormier-Dequaire[1], S. Buro[2], K. Tahiri[3], G. Mangone[2], J. Kraemmer[2], A. Welaratne[4], C. Karachi[5], A. Brice[2], M.-L. Welter[6], J.-C. Corvol[1]

[1]Pitié-Salpétrière Hospital, Université Pierre et Marie Curie-Paris 6, Centre de recherche de l'Institut du Cerveau et de la Moelle épinière, INSERM UMRS_1127, CIC_1422, Département de Neurologie, APHP, Paris, France, [2]Pitié-Salpétrière Hospital, Université Pierre et Marie Curie-Paris 6, Centre de recherche de l'Institut du Cerveau et de la Moelle épinière, INSERM UMRS_1127, CIC_1422, APHP, Paris, France, [3]Pitié-Salpêtrière Hospital,Université Pierre et Marie Curie Paris 6 , Pitié-Salpêtrière Hospital, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Paris, France, [4]Pitié-Salpétrière Hospital, Département de neurologie, APHP, Paris, France, [5]Département de Neurochirurgie, [6]Pitié-Salpétrière Hospital, Université Pierre et Marie Curie-Paris 6, Centre de recherche de l'Institut du Cerveau et de la Moelle épinière, INSERM UMRS_975, CIC_1422, Département de Neurologie, APHP, Paris, France

Background and aims: DBS-STN is proposed to PD patients at motor fluctuation stage and has been shown to alleviate motor symptoms. However, some patients have poor outcome. COMT genotype modifies dopa biodisponibility, dyskinesia, working memory. Our objective was to evaluate its influence on DBS-STN response.

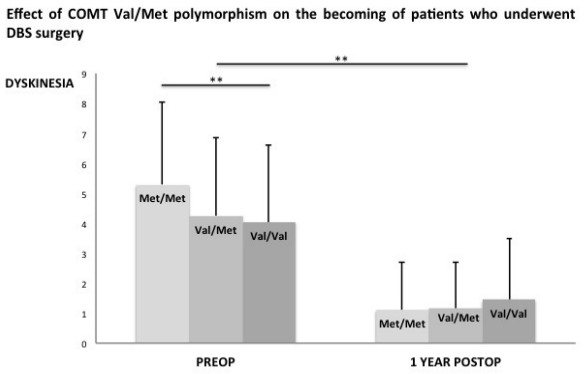
Methods: We compared assessments preoperative and 12 months after DBS-STN in PD patients. The COMT Valine (Val) 158 Methionine (Met) polymorphism was analyzed by allelic discrimination Taqman®assay. Statistical analyses were performed with Statistica®software.

Results: Between 1996 and 2009, 309 PD patients underwent DBS-STN surgery. Among them, 257 were genotyped for the polymorphism. 63 were Met/Met, 124 Val/Met, 70 Val/Val. At baseline, we observed higher scores of UPDRS IV in Met allele carriers and an allele dose effect (Met/Met 10.0 (±3.8), Met/Val 9.1 (±3.3), Val/Val 8.8 (±3.3), p=0.005), mainly due to dyskinesia subscores (p=0.006). Patients with the Val/Val genotype had higher global cognitive efficiency scores (139.0 (±4.8) vs 137.6 (±10.1), p=0.03). After surgery, we observed a difference for UPDRS IV (p=0.003) and dyskinesia subscores (p=0.0002) with a greater decrease in Met allele carriers, an allele dose effect (Met/Met -7.6 (±4.6), Met/Val -7.0 (±4.0), Val/Val -6.1 (±4.2), p=0.005), and an interaction between the effects of DBS and COMT genotype on dyskinesia (p=0.03).

	Met/Met (n=63)	Val/Met (n=124)	Val/Val (n=70)
Age, years	54,2 (9,5)	55,5 (8,8)	55,0 (10,2)
Sex ratio, M/F	39/24	72/52	48/22
Age at onset, years	43,9 (7,1)	42,7 (9,3)	43,0 (9,3)
Disease duration, years	12,1 (4,7)	13,2 (6,4)	12,0 (4,5)
Dopa equivalent dose	1159 (475)	1120 (537)	1136 (469)

Table
Title : Patient characteristics
Legend : Values are mean (standard deviation)

Patient characteristics



Effect of COMT Val/Met polymorphism on the becoming of patients who underwent DBS surgery

Conclusion: Our study confirms the influence of COMT genotype on dyskinesia and cognition in PD patients. A greater diminution of dyskinesia under DBS-STN in Met/Met patients was observed, suggesting an interaction of COMT genotype with DBS STN response on dyskinesia.

Disclosure: Nothing to disclose

P2152

Is there a confounding effect of age on deep brain stimulation in patients with Parkinson's disease (comparison with the EARLYSTIM study)?

V. Cozac[1], M. Chaturvedi[1], H. Bousleiman[2], F. Hatz[1], A. Meyer[1], N. Schwarz[1], R. Zimmermann[1], U. Gschwandtner[1], P. Fuhr[1]

[1]Universitätsspital Basel, Neurology and Neurophysiology, Basel, Switzerland, [2]University of Basel, Swiss Tropical and Public Health Institute, Basel, Switzerland

Background and aims: To investigate the risks of deep brain stimulation in PD patients of relatively old age (older than 60 years).

Methodst: A retrospective sample of 33 patients with idiopathic PD who underwent DBS in Basel and Bern, Switzerland (age at operation: median 60.6y±9.7; 13 females) was investigated (Basel group). Mean period of follow-up after surgery was 25.9 months. Serious adverse events (SAE) were defined as any event leading to death, disability, prolonged or new hospitalization, according to the Medical Dictionary for Regulatory Activities, Version 14.1. We compared the outcome in the Basel group with the EARLYSTIM trial (Schuepbach et al., 2013) with a neurostimulation group (age: median 52.9±6.6 years) and a best medical treatment group (age: median 52.2±6.1 years). Chi-square test was used for statistical analysis.

Results: A total of 17 patients (51.5%) in the Basel group had at least one SAE. There was no difference in overall frequency of SAE between the groups, but SAE related to psychosis/hallucination ($p<0.001$) were significantly different between the Basel group and the EARLYSTIM groups. One patient from Basel group deceased during the follow up period. In addition there were more reoperation cases in the Basel group ($p=0.02$) than in EARLYSTIM group.

Conclusion: While the gross profile of SAE is similar in older and younger patients treated with DBS, the incidence of psychosis and reoperations is higher in older patients. Older patients require increased attention to risk factors for neuropsychiatric consequences of DBS.

Disclosure: Nothing to disclose

P2153

Efficacy of sublingual apomorphine (APL-130277) for the treatment of "Off" episodes in patients with Parkinson's disease

R.A. Hauser[1], J. Dubow[2], B. Dzyngel[2], T. Bilbault[2], A. Giovinazzo[2], A. Agro[2]

[1]USF Health Byrd Parkinson's Disease and Movement Disorders Center of Excellence, Tampa, USA, [2]Cynapsus Therapeutics, Toronto, Canada

Background and aims: Parkinson's disease (PD) patients suffer from a variety of "Off" episodes as the disease progresses. APL-130277 (APL) is a soluble film strip that sublingually delivers apomorphine rapidly through absorption from the oral cavity. This study evaluated the efficacy of single treatments of APL-130277 in patients with PD.

Methods: This was a phase 2, open-label, single-arm study. PD patients with at least one "Off" episode per day and >2 hours of total daily "Off" time were included. Patients were initially administered APL 10mg in the morning "Off" state. If a satisfactory response was not seen, APL was increased in 5 mg increments until a clinically meaningful "On" was achieved, to a maximum dose of 30 mg. Change in MDS UPDRS Part III was evaluated from pre-dose morning "Off" state to 15, 30, 45, 60 and 90 minutes post-dose.

Results: Baseline demographic data are presented in Table 1. Fifteen of 19 patients achieved a full "On". Mean change from pre-dose to post-dose MDS-UPDRS Part III is presented in Figure 1 and Mean percent change in MDS-UPDRS Part III is presented in Figure 2.

Mean Age	61.5 (48-79)
Male: Female	14(73.7%):5(26.3%)
Modified Hoehn and Yahr	2.2 (1-3)
Mean # of Daily "Off" Episodes	3.9 (1-7)
Mean # of PD Medications	3.0 (1-5)
Mean Daily Levodopa Dose (mg)	836.8 (100-1500)
Mean # of Levodopa Doses Per Day	5.3 (1-12)

Table 1: Baseline Demographic Data

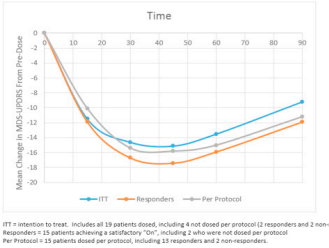


Figure 1: Change in MDS-UPDRS Part III Over Time Following APL-130277 Administration

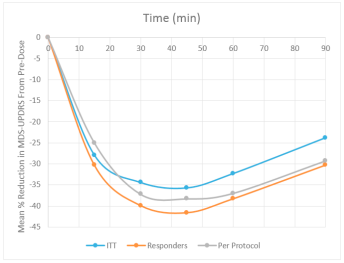


Figure 2: Percent Change in MDS-UPDRS Part III Over Time Following APL-130277 Administration

Conclusion: APL provided rapid, clinically meaningful improvement in MDS-UPDRS Part III scores for PD patients in the "Off" state. Much of the benefit was sustained through 90 minutes. A range of doses were utilized but over half responded to the two lowest doses of APL (10 and 15 mg). APL-130277 may be an effective, easy to administer medication for the on-demand management of "Off" episodes in PD patients.

Disclosure: RAH was an investigator and has received compensation from Cynapsus Therapeutics for research activities. JD, BD, TB, AG and AA are employees of Cynapsus Therapeutics and hold stock or stock options.

P2154

Safety of sublingual apomorphine (APL-130277) for the treatment of OFF episodes in patients with Parkinson's disease.

S. Isaacson[1], J. Dubow[2], B. Dzyngel[2], T. Bilbault[2], A. Giovinazzo[3], A. Agro[3]

[1]Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, USA, [2]Cynapsus Therapeutics, [3]Cynapsus Therapeutics, Toronto, Canada

Background and aims: Parkinson's disease (PD) patients suffer from a variety of predictable and unpredictable OFF episodes throughout the disease duration. APL-130277 (APL) is a soluble film strip that sub-lingually delivers apomorphine rapidly through absorption from the oral cavity mucosa. This study evaluated the safety of single treatments of APL-130277 for the management of OFF episodes in PD.

Methods: This was a phase 2, open-label, single-arm study. PD patients with at least one OFF episode per day and >2 hours of total daily OFF time were included. Patients were initially administered APL 10 mg in the morning OFF state. If a satisfactory response was not seen, APL was increased in 5 mg increments until a clinically meaningful ON was achieved, to a maximum dose of 30 mg.

Results: 19 subjects received 77 total doses of APL 10-30 mg. Overall, 13 (68.4%) patients experienced an AE, with most experiencing mild AEs (Table 1). The most common AEs were dizziness (7/19, 36.8%), somnolence (6/19, 31.6%), nausea (4/19, 21.1%) and yawning (3/19, 15.8%) (Table 2). The most common AEs by dose are presented in Figure 1. One subject had an unrelated serious AE of dysphagia.

Preferred Term	Any AE*	Mild AE	Moderate AE	Severe AE	Related* AE
N=19	N (%)	N (%)	N (%)	N (%)	N (%)
Dizziness	7 (36.8)	7 (36.8)	0	0	5 (26.3)
Somnolence	6 (31.6)	3 (15.8)	3 (15.8)	1 (5.3)	5 (26.3)
Nausea	4 (21.1)	4 (21.1)	1 (5.3)	0	4 (21.1)
Yawning	3 (15.8)	3 (15.8)	0	0	3 (15.8)
Headache	2 (10.5)	2 (10.5)	0	0	1 (5.3)
Hyperhidrosis	2 (10.5)	2 (10.5)	0	0	2 (10.5)

*Deemed certainly, probably or possibly related to APL by the Investigator

Table 2: Treatment Emergent AEs in 2 or More Patients

N=19	N (%)
Any AE	13 (68.4)
Mild AE	13 (68.4)
Moderate AE	4 (21.1)
Severe AE	2 (10.5)
Any Related* AE	11 (57.9)
Any Serious AE	1 (5.3)

*Deemed certainly, probably or possibly related to APL by the Investigator

Table 1: Overview of AEs with APL-130277

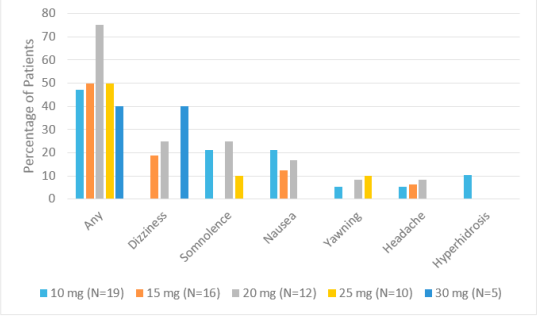


Figure 1: AEs in 2 or More Patients by Dose

Conclusion: APL was safe and well tolerated in PD patients with OFF episodes. The most common AEs were mild or moderate, and are commonly associated with dopaminergic medications and/or apomorphine. This trial suggests sublingual APL-130277 has demonstrated tolerability and was safe in PD patients with OFF episodes. Longer phase 3 studies are planned to assess efficacy, tolerability, and safety.

Disclosure: SI was an investigator and has received compensation from Cynapsus for research activities. JD, BD, TB, AG, and AA are employees of Cynapsus Therapeutics and hold stock or stock options.

P2155

Efficacy of apomorphine subcutaneous injections for the management of morning akinesia in Parkinson's disease

S. Isaacson
Boca Raton, USA

Background and aims: Patients with Parkinson's disease (PD) and motor fluctuations often have delayed time-to-on (TTO) after a dose of oral L-dopa. Delayed TTO can be due to gastrointestinal (GI) factors impairing L-dopa absorption. Delivery of non-oral (subcutaneous) medication may provide a more rapid and predictable response by avoiding the GI system. This open-label study assessed the effect of subcutaneous injection of apomorphine (APO) on first dose TTO in PD patients with morning akinesia.

Methods: Subjects recorded their TTO following each morning dose of L-dopa for 7-days. Subjects who met inclusion criteria of >45 minute delay for ≥3 of 7 days were then titrated to an APO "optimal dose". Subjects then recorded their TTO following each morning dose of APO for 7-days. Primary outcome: Mean TTO comparing APO treatment period versus baseline L-dopa period.

Results: The full analysis set included 88 subjects. Mean TTO reduced from 60.86±18.11 minutes after L-dopa to 23.72±14.55 minutes after APO ($p<0.0001$). Significant improvements were also found in PGI, CGI, & EQ-5L-3D scales. Dose failures (defined as >60min TTO) were reported for 144/310 (46%) completed diary entries during the L-dopa baseline week, but only 20/307 (7%) diary entries following APO. Most common AEs were nausea, dizziness and orthostatic hypotension (most AEs were mild/moderate and occurred during APO-titration).

Conclusion: In patients with delayed TTO following their morning L-dopa dose, subcutaneous APO injections provided a robust motor improvement that was rapid, reliable and safe. Dose failures were significantly reduced, and global impression and quality of life scales also improved.

Disclosure: Study supported by US WorldMeds.

MS and related disorders 4

P2156

Gabaergic and glutamatergic synaptic transmissions are altered after cuprizone exposure: implication for schizophrenia and demyelinating diseases.

C. Motta[1], V. Studer[1], D. Fresegna[2], A. Gentile[2], S. Bullitta[2], E. Chiarello[1], S. Gelibter[1], D. Centonze[1], S. Rossi[1]
[1]Tor Vergata University, Rome, Italy, [2]IRCCS Santa Lucia, Rome, Italy

Background and aims: Growing evidence suggests the involvement of inflammatory and subtle demyelinating processes in the pathophysiology of schizophrenia. Behavioral abnormalities relevant to some schizophrenia symptoms have been reported during exposure to cuprizone, a copper chelator agent selectively toxic to oligodendrocytes. While associating white matter damage to the behavioral abnormalities, these previous studies did not rule out the possible impairment in neuronal functions in cuprizone-exposed mice.

Methods: After short-term exposure to cuprizone (0.2% for 1 week), behavioral tests, patch-clamp recordings from striatal neurons and Western blot analysis were performed.

Results: A profound derangement of spontaneous synaptic activity was recorded at both pre- and post-synaptic level, differentially involving glutamatergic and GABAergic transmission. The amplitude of GABA-mediated inhibitory currents (sIPSCs) was significantly increased at post-synaptic level, whereas a pre-synaptic reduction of glutamate-mediated excitatory currents (sEPSCs) was observed in corticostriatal slices of cuprizone mice, in parallel to psychotic behavior at the Marble Burying test. Increased GFAP and reduction of synapsin expression, with still normal level of myelin binding protein, APP and Tau protein, indicated early synaptopathy and astrogliosis independent of demyelination and axonal damage. Caffeine, the most commonly self-administered psychoactive substance worldwide, increased sEPSC frequency and reduced sIPSC amplitude in vitro. Coadministration of caffeine prevented both synaptic and behavioral alterations in mice exposed to cuprizone.

Conclusion: Schizophrenia-like behavior is mediated by synaptic alterations and can be prevented by caffeine in cuprizone model.

Disclosure: Nothing to disclose

P2157

The evaluation of the burden on caregivers associated with relapsing-remitting (RRMS) and secondary progressive multiple sclerosis (SPMS) patients across Europe

S. Naoshy[1], C. Watson[1], J. Pike[2], E. Jones[2]
[1]Biogen Idec, Cambridge, USA, [2]Adelphi Real World, Manchester, United Kingdom

Background and aims: Multiple sclerosis (MS) is a chronic inflammatory disease associated with substantial socioeconomic burden on both patients and their caregivers. This study evaluates the burden on caregivers for RRMS and SPMS patients in Europe.

Methods: Data were identified from the Adelphi MS Disease Specific Programme, a cross-sectional study with caregiver-reported data available for 359 RRMS and 106 SPMS patients in Europe (France, Germany, Italy, Spain, UK). Fisher's Exact or Chi-Squared (for categorical outcomes) and Wilcoxon rank-sum test (for numerical outcomes) were used to determine differences between RRMS and SPMS patients.

Results: Caregivers for RRMS and SPMS patients differed significantly in their employment status ($p<0.0001$), as caregivers for SPMS patients are less likely to be employed in full-time positions (34.62% vs 62.50%), more likely to be employed in part-time positions (23.08% vs 16.19%) and unemployed (42.31% vs 21.31%). When employed, a higher proportion of SPMS patient caregivers reported that their job has been affected by their role as a caregiver (58.33% vs 29.24% $p<0.0001$), and more caregivers for SPMS patients stopped work early to care for an MS patient than caregivers of RRMS patients (4.81% vs 0.28% $p=0.0028$).

Conclusion: Across Europe, caregivers for RRMS and SPMS patients experience a high socioeconomic burden as a result of their role as a caregiver. Caregivers for SPMS patients experience a more significant burden than those of RRMS patients, which is reflected in their ability to be employed full-time and effect of their role as a caregiver on their work.

Disclosure: Study sponsored by Biogen Idec.

P2158

Disability and gray matter atrophy in multiple sclerosis patients with no evidence of disease activity: a one-year follow-up study

G. Nygaard[1], E.G. Celius[1], S.A.D.R. Benavent[2], P. Sowa[3], M.W. Gustavsen[1], A.M. Fjell[4], N.I. Landro[4], K.B. Walhovd[4], H.F. Harbo[1]

[1]Oslo University Hospital, Dept of Neurology, Oslo, Norway, [2]Oslo University Hospital, Dept of Ophthalmology, Oslo, Norway, [3]Oslo Univsersity Hospital, Dept of Radiology, Oslo, Norway, [4]Univserity of Oslo, Institute of Psychology, Oslo, Norway

Background and aims: New treatment options have made "no evidence of disease activity" (NEDA; no relapses or disability progression and no new or enlarging lesions on MRI) a potentially viable clinical goal in relapsing-remitting multiple sclerosis (RRMS). We aimed to determine characteristics of NEDA patients in early RRMS and to study whether NEDA could be predicted from baseline examinations.

Methods: We performed a one-year follow-up study of RRMS patients (n=72, mean age 34.3 years, mean disease duration 2.2 years at baseline), treated according to national guidelines, and evaluated neurologically, neuropsychologically and with MRI, including gray matter volumetry. Differences between patients and matched healthy controls (HC; n=61); and between NEDA and non-NEDA patients were evaluated. Predictors for NEDA were assessed with logistic regression.

Results: NEDA was found in 54% of the RRMS patients after one year's observation. Treatment assignment to second line medication (fingolimod or natalizumab) at baseline was the only predictor for NEDA. NEDA patients regressed in disability (EDSS: 2.0-1.7, p=0.003)), while non-NEDA progressed (EDSS: 1.8-2.2, p= 0.036). Cognition and gray matter characteristics were similar between the patient groups, which both had higher subcortical atrophy rates than HC (Annual percent change (standard deviation): NEDA: -0.68(1.12), non-NEDA: -1.18(1.18), HC: -0.30±0.43, significance level of difference: p=0.022 and p<0.001 respectively).

Conclusion: Treatment assignment predicts NEDA in early RRMS, and NEDA patients experience a regression of disability. However, even in NEDA patients, subcortical atrophy rates are higher than in HC, indicating that pathological neurodegeneration takes place. This underlines the need for efficient treatment strategies in early RRMS.

Disclosure: We have received a grant for MRI aquisition and a grant for evaluation of fatigue in MS from Novartis.

P2159

Marital status after the diagnosis of multiple sclerosis

S. Ozkan, O. Ozdemir, D. O. Adapinar

Eskisehir Osmangazi University, Neurology, Eskisehir, Turkey

Background and aims: Multiple sclerosis is a life-limiting and social restrictive disease. Previous reports about marital status of relapsing remitting MS (RRMS) patients reports an increased rate of divorce. This data can be affected by different cultural status. We aimed to investigate the impact of MS on marital breakdown in Turkish RRMS patients.

Methods: 73 RRMS patients (37 women, 36 men) (mean age at diagnosis; 32±4.7 years) who were married during the diagnosis of MS were included the study. Marital status, marriage duration and if divorced, time between the diagnosis and the divorce were questioned. Demographic data, disease status and clinical information were conducted from our records. Crude devorce rate (CDR) per year was calculated.

Results: The rate of divorce during the five years period was 18% and CDR per year was 2.6. Shorter period of marriage before the diagnosis, higher EDSS scores at the divorce date, having only one or no child, female gender were statistically significant risk factors for the divorce. Educational level, relaps rate, age at onset, age at diagnosis were no risk for the cessation of the marriage.

Conclusion: MS patients have a greater risk for divorce than the general population in Turkey (CDR per year for general populaton in 2012 reported by Turkish Statistic Institute was 1.64) and males are more likely to discontinue marriage if their spouse has MS. More severe disability increases the risk. These results suggest that MS patients and and their families need more detailed family counseling and social support than the normal population.

Disclosure: Nothing to disclose

P2160

Cardiac safety and tolerability of fingolimod in relapsing MS patients from the FIRST study who transitioned into the LONGTERMS study

J.A. Palace[1], R. Gold[2], G. Comi[3], Y. Chen[4], D. Tomic[5], L. Kappos[6]

[1]University of Oxford, Oxford, United Kingdom, [2]St. Josef-Hospital and Ruhr-University Bochum, Bochum, Germany, [3]University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy, [4]Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA, [5]Novartis Pharma AG, Basel, Switzerland, [6]University Hospital Basel, Basel, Switzerland

Background and aims: FIRST, a 4-month, open-label, multi-centre study, explored short-term safety and tolerability of fingolimod 0.5 mg in "real-world" relapsing MS patients (N=2417), including those with pre-existing cardiac conditions (PCC). Completers from FIRST were invited to participate in the LONGTERMS study.

Methods: Of 1997 patients transitioning into LONGTERMS, 812 patients were followed for ≥1 year (i.e., ≥365 days) while on fingolimod treatment. Cardiac safety was evaluated in these patients (FIRST-cohort: n=812) and in FIRST-cohort patients with PCC (PCC-subgroup: n=68). Incidence rates (IR) of adverse events (AE) and serious AEs (SAE) per 100 patient-years are reported.

Results: In the FIRST-cohort, 42 patients (IR 2.6) had cardiac AEs, most frequently palpitations (IR 1.3), bradycardia (IR 0.4) and angina pectoris (IR 0.3). Of those, 3 patients (IR 2.2) were in the PCC-subgroup: 1 case each of angina pectoris, palpitation and bradycardia. Hypertension was reported for 49 patients (IR 3.1) in the FIRST-cohort, of which 5 were in the PCC-subgroup (IR 3.9). In total, 3 cardiac SAEs were reported: 1 case each of bradycardia, cardiac disorder and hypertension. No cardiac SAE was reported in the PCC-subgroup. Additional analysis of AEs in early dropouts (<1 year exposure) will also be presented.

Conclusion: These results are in line with the established cardiovascular safety profile of fingolimod. Incidence rates of cardiac events were similar overall and in patients with pre-existing cardiac conditions.

Disclosure: Jacqueline Palace has received support for scientific meetings and honoraria for advisory committees from Merck Serono, Biogen Idec, Novartis, Teva Pharmaceutical Industries Ltd., Chugai Pharmaceutical Co. Ltd., Med-Immune, LLC, and Bayer Schering Pharma, and unrestricted grants from Merck Serono and Bayer Schering Pharma.

P2161

Correlations of cognitive function, neuroimaging and everyday activities in multiple sclerosis

A. Papathanasiou[1], L. Messinis[1], V. Georgiou[2], P. Zabakis[3], P. Papathanasopoulos[1]

[1]University of Patras, Department of Neurology, Patras, Greece, [2]Hellenic Open University, Patras, Patras, Greece, [3]University of Patras, Department of Radiology, Patras, Greece

Background and aims: Cognitive decline is present in 40%-70% of MS patients, affects quality of life and correlates with brain MRI markers

Methods: We evaluated clinically and neuropsychologically 80 patients with MS (50 RRMS, 30 SPMS). Everyday activities were assessed with Instrumental Activities of Daily Living (IADL). Brain MR total lesion volume, thalamic, corpus callosum atrophy and 3rd ventricle width was calculated.

Results: We found 38% of RRMS and 80% of SPMS patients to have cognitive deficits. RRMS cognitively impaired patients had weak correlation with EDSS and MR lesion load ($p<.05$) and strong correlation with all MR atrophy measures ($p<.001$). IADL was highly correlated with psychomotor speed, processing speed, memory and all MR atrophy measures ($p<.001$). SPMS cognitively impaired patients had only weak correlation with 3rd ventricle width ($p<.05$). Using MS patients as single group, regression analysis revealed that low psychomotor speed ($p=.004$) and poor performance on Trail Making Test B (TMT B) ($p=.007$) were the most sensitive predictors of increased physical disability, whereas psychomotor speed predicted impaired every day activities ($p=.001$). Thalamic atrophy was the most sensitive indicator for poor performance on TMT B ($p=.000$), while corpus callosum atrophy predicted slow psychomotor speed ($p=.000$).

Conclusion: We observed a global pattern of cognitive decline, consisting of impairment in information processing speed, followed by executive dysfunction and memory deficits. Psychomotor speed, composite memory and TMT B are the best predictors of physical disability. Thalamic and corpus callosum atrophy are the best predictors of cognitive decline in our patients

Disclosure: Nothing to disclose

P2162

Action naming in multiple sclerosis

D. Passafiume[1], N. Caputi[1], A. Matrella[1], M. Colantonio[2], D. Di Giacomo[2]

[1]University of L'Aquila, Life,Health and Environmental Science, L'Aquila, Italy, [2]University of L'Aquila, Life, Health and Environmental Science, L'Aquila, Italy

Background and aims: Multiple Sclerosis (MS) is characterized by the demyelination of the fibres in the central nervous system and has several motor and cognitive consequences, such as in speed of information processing, memory, attention, and executive functions. A recent study conducted in our laboratory showed MS patients are impaired in recognition of chimerical figures, compared to real objects or animals. Mental imagery and mental representation of the movement are impaired in diseases involving motor system, such as Parkinson's disease, as a consequence of pathologies of the central nervous system.

Aim of the present study was to investigate the performance of patients affected by relapsing/remitting MS in recognizing and naming actions with high movement content compared to actions with low movement content.

Methods: 20 patients affected by Relapsing/Remitting MS and 20 matched healthy subjects (HS), age range 20 to 50 y, were tested with an experimental task composed by 100 stimuli, 50 high-movement and 50 low-movement figures. Each stimulus consisted in the picture of an action; the subjects were asked to name it. All subjects performed an extensive neuropsychological battery in order to assess their cognitive status.

Results: Preliminary analysis showed that MS patients have significantly worst performances in recognizing and naming actions with high movements contents compared to actions with low movements content, while no significative differences were HS group.

Conclusion: Our results seem to confirm our hypothesis: MS patients are impaired in naming high-moviment figures. More analysis will be performed in order to explore the role of EDSS and of the years of illness.

Disclosure: Nothing to disclose

P2163

Patient-reported symptom burden among relapsing remitting multiple sclerosis (RRMS) vs secondary progressive multiple sclerosis patients (SPMS) in Europe

J. Pike[1], C. Watson[2], S. Naoshy[2], E. Jones[1]

[1]Adelphi Real World, Manchester, United Kingdom, [2]Biogen Idec, Cambridge, USA

Background and aims: This study evaluates patient-reported symptoms in RRMS and SPMS patients in Europe.

Methods: Data were identified from Adelphi MS Disease Specific Programme, a cross-sectional study in Europe (France, Germany, Italy, Spain and UK) with patient-reported data available from questionnaires for 881 RRMS and 142 SPMS patients. The Wilcoxon rank-sum test was used to determine differences between RRMS and SPMS patients. Patients reported symptoms as either "mild", "moderate" or "severe" and symptoms that were reported as "moderate" in at least 10% of either RRMS or SPMS patients have been included.

Results: A higher proportion of SPMS patients than RRMS patients reported the following symptoms as "moderate":

Symptom:	Moderate Symptoms		P value
	RRMS	SPMS	
Muscle weakness	14.30%	40.85%	P<0.0001
Numbness or tingling	14.98%	33.80%	P<0.0001
Walking or mobility problems	9.53%	28.17%	P<0.0001
Loss of coordination	7.38%	28.17%	P<0.0001
Fatigue	14.98%	24.65%	P=0.0001
Stiffness/rigidity in muscles	7.95%	21.13%	P<0.0001
Loss of movement in muscles	5.33%	19.72%	P<0.0001
Bladder problems	6.02%	19.72%	P<0.0001
Loss of balance	5.56%	19.01%	P<0.0001
Difficulty concentrating	5.79%	19.01%	P=0.0002
Loss of sensation	6.58%	17.61%	P=0.0019
Spasms or cramps	5.56%	16.20%	P<0.0001
Depression	6.02%	16.20%	P<0.0001
Pain without apparent cause	3.06%	14.08%	P<0.0001
Difficulty controlling eye movement	4.20%	11.97%	P=0.0001
Dizziness/nausea	3.52%	10.56%	P=0.0005
Blurred vision	10.22%	15.49%	P=0.513

Conclusion: There is a high symptom burden experienced by MS patients, with SPMS patients reporting a higher symptom burden than RRMS patients, highlighting the need to prevent patients from progressing from RRMS to SPMS.

Disclosure: Study sponsored by Biogen Idec.

P2164

Durable effect of alemtuzumab on disease activity in patients with relapsing-remitting multiple sclerosis

H. Wiendl[1], D.L. Arnold[2], R.M. Hupperts[3], G. Giovannoni[4], D.H. Margolin[5], L. Kasten[6], E. Havrdova[7]

[1]Department of Neurology, University of Münster, Münster, Germany, [2]NeuroRx Research, Montreal Neurological Institute, McGill University, Montreal, Canada, [3]Orbis Medisch Centrum, Maastricht University Medical Center, Sittard, The Netherlands, [4]Queen Mary University of London, Barts and The London School of Medicine, London, United Kingdom, [5]Genzyme, a Sanofi company, Cambridge, USA, [6]PROMETRIKA LLC, Cambridge, USA, [7]First Medical Faculty, Charles University in Prague, Prague, Czech Republic

Background and aims: In active relapsing-remitting multiple sclerosis patients who were treatment-naïve (CARE-MS I; NCT00530348) or had inadequate efficacy response to prior therapy (CARE-MS II; NCT00548405), greater proportions of patients had no evidence of disease activity (NEDA) with alemtuzumab versus subcutaneous interferon beta-1a over 2 years. These proportions remained stable in year 3. This analysis examined NEDA in alemtuzumab-treated patients during year 4 of CARE-MS studies.

Methods: In CARE-MS I (treatment-naive) and II (patients with ≥1 relapse after ≥6 months of prior therapy), the alemtuzumab 12-mg group received 2 annual treatment courses; in the extension study (NCT00930553), patients could receive as-needed alemtuzumab retreatment ≥1 year apart. NEDA definition: absence of relapse, 6-month sustained accumulation of disability (Expanded Disability Status Scale score increase from baseline of ≥1.0 [≥1.5 if baseline EDSS=0]), new/enlarging T2 lesions, and gadolinium-enhancing lesions.

Results: In CARE-MS I and II, 324 and 336 alemtuzumab patients were available for analysis in year 4, respectively; 73% and 68% received only the initial 2 courses. Proportion of alemtuzumab patients in CARE-MS I and II achieving NEDA in year 4 was 60.2% and 54.5%, respectively (61.7% and 52.9% in year 3). Consistent with the overall study population, most patients achieving NEDA did not require alemtuzumab retreatment in years 3 and 4.

Conclusion: The proportion of alemtuzumab patients achieving NEDA remained stable in years 3 and 4 of CARE-MS studies, irrespective of treatment-naive status or inadequate efficacy response to prior therapy. This durable effect was observed despite most patients not receiving alemtuzumab during the last 3 years of observation.

Disclosure: Study supported by Genzyme, a Sanofi company, and Bayer Healthcare Pharmaceuticals.

Neurogenetics 2

P2165

Intermediate expansions in ataxia genes, ATXN2 and FMR1, associated with Parkinson's disease

N. Abramycheva, E. Fedotova, M. Stepanova, A. Moroz, S. Klyushnikov, S. Illarioshkin
Research Center of Neurology, Neurogenetics, Moscow, Russian Federation

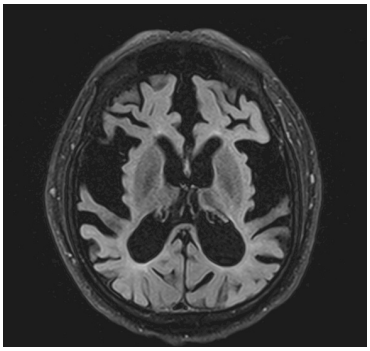
Background and aims: A full mutation of >34 CAG repeats in exon 1 of ATXN2 gene causes spinocerebellar ataxia type 2. A full mutation of >200 CGG repeats in 5'-untranslated region of FMR1 gene causes fragile X syndrome, while a premutation of 55-200 repeats in the same gene results in fragile X-associated tremor/ataxia. Recently, several reports have suggested the association of the expansions in ATXN2 and FMR1 with another neurodegenerative disorder, Parkinson disease (PD). The aim of this study was to estimate the prevalence of ATXN2 and FMR1 expansions in a cohort of PD patients in Russian population.
Methods: Genetic analysis for expanded repeats in the ATXN2 gene was carried out in 445 Russian patients with PD and in 353 ethnically-matched healthy control subjects. The expansion in FMR1 gene was studied in 68 patients with PD and 95 control subjects. Both expansions were assessed by fragment analysis using ABI Prism 3130 (Applied Biosystems/HITACHI).
Results: The intermediate expansion of 28-32 repeats in ATXN2 was found in 18 (4.04%) cases with PD and 5 (1.4%) control subjects (OR=2.93, 95% CI 1.01-9.12, p=0.046). The intermediate expansion of 39-43 repeats in FMR1 was identified in 11 (16.2%) PD patients and 3 (3.2%) healthy controls (OR= 5.9, 95% CI 1.44-28.05, p=0.004).
Conclusion: Our study clearly showed that the intermediate expansions in ataxia genes ATXN2 and FMR1 are associated with PD in Russian population.
This study was supported by the Russian Foundation for Basic Research (grant # 13-04-01718a).
Disclosure: Nothing to disclose

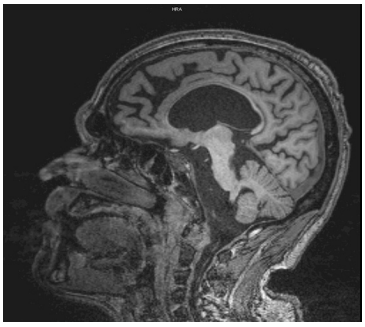
P2166

Hereditary spastic paraplegias - characterization of a family with a SPG11 mutation

J. Afonso Ribeiro, L. Almendra, C. Januário
Centro Hospitalar e Universitário de Coimbra, Neurology, Coimbra, Portugal

Background and aims: Hereditary Spastic Paraplegias (HSP) are a group of clinical and genetical heterogeneous diseases, with an European prevalence estimated in 3-10/100 000 inhabitants. Mutations in SPG11 (chromosome 15q) represent one of the most common causes of AR-HSP in Mediterranean countries and are associated with a thin corpus callosum (TCC), mental retardation and early age at onset.
Methods: Case Report
Results: We report a Portuguese family with two male individuals affected, from a kindred of four children, with no history of consanguinity. They developed mental retardation and progressive changes in locomotion in their first decade of life. At first clinical observation, cognitive disabilities and spastic paraparesis were observed. Nowadays, with 20 years of disease evolution, they present a phenotype of complex HSP, characterized by severe mental impairment, eye movement limitation, anarthria, cervical and upper limbs hypotonia, and marked atrophy of thenar and hypothenar muscles. There are no clinical or electrophysiologic signs of peripheral neuropathy. Recent cerebral MRI shows TCC and marked cerebral atrophy, particularly of the frontoparietal cortex. The molecular study of the affected patients revealed two heterozygous mutations c.6206-?_6343+?del and c.733_734del, being the first described for the first time. The mother presents one of the mutant alleles, and one of the non-affected siblings is a carrier of one other allele.


MRI showing marked atrophy of parietal cortex


MRI showing TCC


Atrophy of thenar muscles of hand

Conclusion: Several mutations are nowadays recognized as a cause of HSP with mutations in SPG11. This family highlights the high degree of disability of this disease and enforces the need for early recognition of the pathology.
Disclosure: Nothing to disclose

P2167

A novel mutation in the HTRA1 gene in a Turkish family with CARASIL

C.E. Bekircan-Kurt[1], C. Koşukçu[2], A.T. Kurne[3], M.A. Topçuoğlu[3], S. Erdem-Özdamar[3], R. Göçmen[4], N. Akarsu[2]

[1]Ankara, Turkey, [2]Hacettepe University, Medical Genetics, Ankara, Turkey, [3]Hacettepe University, Neurology, Ankara, Turkey, [4]Hacettepe University, Radiology, Ankara, Turkey

Background and aims: CADASIL and CARASIL are autosomal dominant and recessive types of small vessel diseases with subcortical infarcts and leukoencephalopathy. Clinical presentations are similar in both however, migraine followed by strokes are prominent in CADASIL whereas gait disturbances, lumbago and alopecia are characteristics of CARASIL. CARASIL associated with homozygous mutations in HTRA1 is rare and only few families have been reported. Heterozygous NOTCH3 mutations cause CADASIL. Here, we report an additional HTRA1 associated Turkish family.

Methods: Direct sequencing of HTRA1 and NOTCH3 genes were performed in a consanguineous family with three affected and four normal sibs. The index case was a 39-year-old female with migraine, hemiparesis, ataxia, cognitive decline and alopecia. MRI showed infarction in right frontal lobe, cerebellum, pons and medulla. Six years later, she had hematoma in right mesencephalon, pons and cerebellum. Her 42-year-old sister experienced migraine and dysarthria. MRI depicted white matter hyperintensity. She has now severe dysarthria and never experienced stroke. The other 55-year-old sister had difficulty in speaking, left hemiparesis, memory dysfunction and white matter hyperintensity with lobar microbleedings in MRI.

Results: HTRA1 mutation analysis identified a homozygote mutation that causes the substitution of a conserved proline by leucine at amino acid position 275 (Pro275Leu)/(c.824C>T). Two normal sibs who have migraine, depression and disc degeneration and parents were heterozygous for this mutation. NOTCH3 mutation analysis was normal.

Conclusion: Here we report a novel missense mutation of HTRA1 gene in CARASIL. Intrafamilial clinical variation is evident. Migraine and disc degenerations could be confounding factors on the diagnosis.

Disclosure: Nothing to disclose

P2168

Novel PANK2 mutation in the first Greek case with pantothenate-kinase-associated neurodegeneration presenting with adult-onset progressive focal dystonia

A. Bougea[1], C. Yapijakis[2], G. Paraskevas[2], E. Stamboulis[2], E. Kapaki[2]

[1]Athens, Greece, [2]National and Kapodistrian University of Athens. Athens, Greece, [1]st Department of Neurology, Medical School, Athens, Greece

Background and aims: Pantothenate kinase-associated neurodegeneration (PKAN) is the most common autosomal recessive form of neurodegeneration with brain iron accumulation (NBIA). Less than ten mutations in PANK2 gene (20p13) are responsible for classic and atypical cases. We report here the first Greek case of atypical PKAN, confirmed by molecular analysis that revealed two trans-acting mutations.

Case Report: We present a 25-year-old Greek male with a 3-year history of focal orobucal dystonia and dysarthria, who was diagnosed with atypical PKAN according the NBIA criteria of Dooling and Swaiman. His brain MRI scan revealed the characteristic "eye-of-the-tiger" sign, but cognitive and laboratory evaluation were normal. There was no positive family history and the patient's parents originate from different parts of Greece. In the patient's blood DNA sample the seven exons of PANK2, including the exon/ intron boundaries, were sequenced. The detected mutations were verified by combination of PCR and rectriction enzyme analysis in the patient and were also investigated in blood DNA samples of the patient's mother and of 100 healthy Greeks.

Results: The patient had two mutations in combined heterozygosity (1424T>C, c.1583T>C), in exons 5 and 6 of PANK2, respectively. His mother was a carrier of one mutation only (c.1583T>C) previously reported in PKAN patients. Both mutations were absent in the database of single nucleotide polymorphisms of 1,000 genomes, and were not observed by restriction digestion analysis in the DNA samples of 100 healthy controls.

Conclusion: Our findings highlight the possible role of rare variants contributing to disease risk and possibly to variable clinical phenotype.

Disclosure: Nothing to disclose

P2169

Chromosome 22q11 duplication and a novel NF1 gene mutation in a patient with Neurofibromatosis type 1

G.J. Braathen, A.K. Eek, K.O. Clausen, K. Tveten, Ø.L. Holla, Ø.L. Busk
Telemark Hospital, Department of Laboratory Medicine, Section of Medical Genetics, Skien, Norway

Background and aims: Neurofibromatosis type I (NF1) is characterized by café au lait spots, fibromatous tumors of the skin and there is an increased susceptibility to tumor development. NF1 is an autosomal dominant disorder with an incidence of about 1 in 3,000.

During the last 15 years several families with the chromosome 22q11 duplication syndrome have been described. The phenotypic features are diverse with mental retardation, learning difficulties, speech impairment, ADHD, hypotonia and the most frequent dysmorphic features are hypertelorism, broad flat nose, micrognathia and dysplastic ears. However, the phenotype may vary from mild to severe ranging from no abnormality or mild learning disabilities to severe mental retardation with multiple congenital malformations.

Case Report: A patient with several neurofibromas, 6-8 cafè au lait spots and mental retardation was investigated.

Results: Chromosomal analysis was normal while Array comparative genomic hybridization (ACGH) revealed the chromosome 22q11 duplication. Targeted High-Throughput Sequencing (HTS) for NF genes identified the novel heterozygous NF1 missense mutation.

Conclusion: To our knowledge, this is the first case ever reported with the chromosome 22q11 duplication syndrome and NF1 combined.

To our knowledge, the NF1 mutation is novel.

Disclosure: Nothing to disclose

P2170

Social cognition impairment in SPG4 spastic paraplegia.

L. Chamard, S. Ferreira, M. Silvestre, E. Berger, E. Magnin
CHRU Jean Minjoz, Besançon, France

Background and aims: Mutations and deletions in the SPAST gene are known to cause cognitive impairment. A subtle decline is usually reported. However, few studies have used extensive cognitive assessments to measure it. The aim of our study was to describe neuropsychological profile of SPG4 subjects.

Methods: 6 affected and 1 asymptomatic subjects (carriers of an identified mutation in the SPAST gene) from two families were included (figure 1). Two are monozygotic twins. Mean age at examination was 52.8 (±9.5). No difficulty in daily living activity was reported.

Systematic neurological and extensive neuropsychological assessments including the mini-Social cognition and Emotional Assessment were performed. The disability stage (figure 2) was systematically fulfilled. We count the number of different cognitive domains.

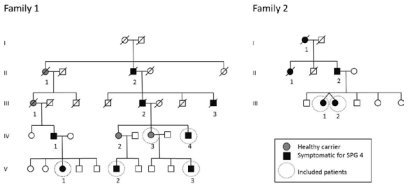


Figure 1: Pedigrees

0	No functional handicap
1	No functional handicap but signs at examination
2	Mild, able to run, walking unlimited
3	Moderate, unable to run, limited walking without aid
4	Severe, walking with one stick
5	Walking with two sticks
6	Unable to walk, requiring wheelchair
7	Confined to bed

Figure 2: Disability Stage

Results: The mean score of the Mini-Mental State Examination at 26.6 (±3.8) was normal. However, all subjects had executive disorders, 86 % had social cognition impairment, 71% apraxia, 57% episodic memory impairment. No language disorder, mental retardation or dementia was found. For the first time, social cognition impairment was reported. Patients with more impaired cognition had higher disability. These patients had a longer disease course. The monozygotic twins had different neuropsychological profile that might be explained by epigenetic phenomena.

Conclusion: This study suggests that all SPG4 subjects, including those who are asymptomatic for spastic paraplegia, have cognitive impairment. Social cognition impairment, reported for the first time, may be frequent. Therefore, this function must be systematically assessed. A neurodegenerative process may be involved in SPG4 relative disorders depending upon the duration of the disease.

Disclosure: Nothing to disclose

P2171

CHCHD10 gene mutations in Italian sporadic and familial ALS patients

A. Chiò[1], A. Calvo[2], M. Barberis[2], M. Brunetti[3], G. Restagno[4], G. Mora[5], M. Sabatelli[6], S. Battistini[7], F. Conforti[8], C. Caponnetto[9], J. Mandrioli[10], P. Mandich[9], M. Zollino[6], G. Borghero[11], M.R. Murru[11], M.R. Monsurrò[12], P. Volanti[13], I. Simone[14], G. Logroscino[14], F. Salvi[15], F. Logullo[16], S. Penco[17], C. Lunetta[18], B. Traynor[19]
[1]Turin, Italy, [2]Univ of Torino, Turin, Italy, [3]Univ of Torino, Univ of Torino, Italy, [4]AOU Città della Salute e della Scienza, Turin, Italy, [5]Fondazione Maugeri Milano, Milan, Italy, [6]Univ Cattolica di Roma, Rome, Italy, [7]Univ. of Siena, Sienna, Italy, [8]CNR Mangone, Mangone, Italy, [9]Univ. of Genua, Genoa, Italy, [10]Univ. of Modena, Modena, Italy, [11]Univ. of Cagliari, Cagliari, Italy, [12]Univ. of Naples, Naples, Italy, [13]Fond Maugeri Mistretta, Mistretta, Italy, [14]Univ. of Bari, Bari, Italy, [15]Univ. of Bologna, Bologna, Italy, [16]Univ. of Ancona, Ancona, Italy, [17]Ospedale Niguarda, Milan, Italy, [18]Centro Clinico NEMO, Milan, Italy, [19]NIA, NIH, Bethesda, USA

Background and aims: Missense mutations of the CHCHD10 gene have been recently reported to be related to familial amyotrophic lateral sclerosis and frontotemporal dementia in a large family of Spanish origin. No data on ALS Italian population have been reported so far. Our aim was to assess the frequency of CHCHD10 gene mutation in a large series of fALS and sALS of Italian origin.

Methods: 64 unrelated fALS patients and 224 apparently sALS patients, negative for C9ORF72, SOD1, TADBP and FUS mutations were assessed. A total of 165 healthy controls were also assessed. The 4 coding exons and flanking intronic regions of CHCHD10 were amplified by PCR and analyzed by DHPLC . PCR products with heteroduplex profiles were sequenced on an ABI 3130 sequencer.

Results: Three cases (1 fALS and 2 apparently sALS) (1.0%) carried a c.100C>T (p.Pro34Ser) heterozygous variant in the exon 2 of the CHCHD10 gene. This mutation was not detected in the control population. The mutation resulted to be pathogenetic according to in silico analyses. Two other aminoacidic substitutions (p.Ala92Thr and p.Pro96Thr) were also found in apparently sporadic patients. Both these substitution are likely to represent benign polymorphisms. Clinically, the cases are classical ALS, without cognitive involvement or cerebellar signs.

Conclusion: CHCHD10 missense mutations have been found in about 1% of Italian ALS patients. The same mutation has been recently described in 2 apparently sporadic French ALS patients (Chaussenot et al, 2014). CHCDH10 mutations seem to be concentrated in exon 2 and can cause ALS with a classic phenotype.

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P2172

A novel TOR1A mutation in a Serbian patient with cervical dystonia

V. Dobricic[1], N.D. Kresojevic[1], M. Zarkovic[2], A. Tomic[1], M. Svetel[1], I. Novakovic[2], V.S. Kostic[1]
[1]Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia, Belgrade, Serbia, [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Background and aims: In addition to the most frequent TOR1A/DYT1 mutation (c.904_906delGAG), there is a growing number of rare TOR1A sequence variants that is being found in patients with dystonia. For most of them functional characterization demonstrated TOR1A functional changes on different levels, implying that genetic testing of dystonia patients should not be limited only to screening for c.904_906delGAG.

Methods: We screened a total number of 519 Serbian patients with dystonia (463 isolated, 56 combined) for the changes in the TOR1A gene by direct DNA sequencing. Additionally, 110 neurologically healthy individuals were tested as control group.

Results: One novel likely pathogenic TOR1A substitution (c.385G>A, p.V129I) was detected in a sporadic cervical dystonia patient. Another four novel variants, two coding synonymous substitutions (c.795T>C, p.(Y265=); c.984T>C, p.(Y328=)) and two noncoding substitutions (c.-59T>C; c.-4G>C), were detected in a single patient each.

Conclusion: Our data expand the genotypic spectrum of TOR1A and highlight the importance of the whole TOR1A coding sequence analysis in establishing the molecular diagnosis for patients with dystonia.

Disclosure: Nothing to disclose

P2173

Abstract cancelled

Neuroimmunology 1

P2174

Anti-neurofilament antibodies and neurofilament phosphoforms in two cases of anti-NMDAr encephalitis

P. Annunziata, C. Cioni, G. Masi
University of Siena, Medicine, Surgery and Neurosciences, Sienna, Italy

Background and aims: Anti-NMDAr encephalitis is an autoimmune neurological disorder involving the NMDA receptor. To test whether autoimmunity directed to other neural components is associated with anti-NMDAr antibodies, anti-neurofilament (NFL) antibodies and NFL were measured in two cases of anti-NMDAr encephalitis.

Methods: Anti-heavy and light NFL IgG and heavy NFL phosphoforms were measured by ELISA in serum and cerebrospinal fluid (CSF) from two women affected by anti-NMDAr encephalitis, one associated with ovarian teratoma and one other with HSV-1 infection. Serum and CSF samples were longitudinally collected during the disease course and clinical outcome was assessed with the modified Rankin scale. As control groups, serum and CSF samples from 6 subjects with clinically isolated syndrome, 5 with other viral encephalitis and 5 with dementias were included.

Results: Significantly higher serum and CSF levels of anti-heavy and light NFL IgG as well as phosphorylated NFL were found as compared with control groups ($P<0.001$). A statistical trend towards a correlation of serum anti-heavy NFL IgG with the clinical outcome was found ($r=0.79$; $p=0.058$). Moreover, there was a very significant correlation of serum anti-heavy NFL IgG with serum phosphorylated ($r=0.96$; $p=0.0027$) and hypophosphorylated NFL ($r=0.93$; $p=0.007$).

Conclusion: These findings demonstrate that, in these two cases of anti-NMDAr encephalitis, autoimmunity directed against heavy NFL correlating with clinical course occurred, raising the hypothesis that these antibodies may play a role in the disease pathogenesis in association with anti-NMDAr autoimmunity.

Disclosure: Nothing to disclose

P2175

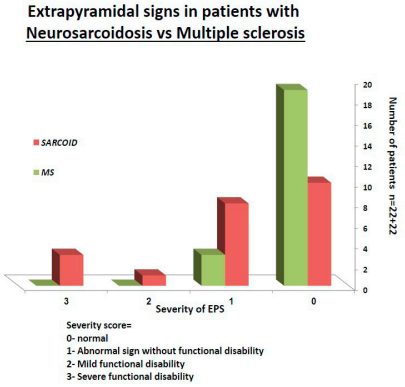
Extrapyramidal signs in patients with neurosarcoidosis

T. Drori[1], O. S. Cohen[2], G. Givaty[1], A. Eldar-Hersalis[1], M. Lidar[3], P. Langevitz[3], Y. Shoenfled[4], A. Achiron[5], J. Chapman[1]
[1]Department of Neurology, Sheba medical center, Tel Hashomer, Israel, [2]Parkinson's disease amd movement disorders clnic, Tel Hashomer, Israel, [3]- Rheumatology Unit. Sheba Medical Center, Tel Hashomer, Israel, [4]Zabludowicz center for Autoimmune diseases, Tel Hashomer, Israel, [5]Center of Multiple Sclerosis, Sheba Medical Center, Tel-HaShomer, Israel

Background and aims: Sarcoidosis is a systemic autoimmune disease associated with a variety of neurological manifestations.

Objectives: To systematically assess the frequency of extrapyramidal signs (EPS) in patients with neurosarcoidosis (NS) and compare them to the prevalence in patients with multiple sclerosis (MS), as representative of an autoimmune disease mainly affecting the white matter.

Methods: A neurological exam was performed on patients diagnosed with MS or NS, with a special emphasis on extrapyramidal signs such as bradykinesia, rigidity, resting tremor and postural instability.



Results: 22 patients with NS and 22 patients with MS matched for age and gender were surveyed. Signs were graded according to severity, ranging from 0 to 3: 0- normal, 1- Abnormal signs without functional disability, 2- Abnormal signs with mild functional disability, 3- Major functional disability. Brain MRI was assessed for focal lesions. In three out of 22 patients with NS we identified severe parkinsonism, fulfilling the criteria of Parkinson's disease according to the "UK Brain Bank" criteria. None of the patients had lesions affecting basal ganglia or brain stem on MRI. Two patients were classified as having mild signs, and nine had abnormal signs on exam without functional disability. In the MS group, three patients had abnormal signs only, and the rest had no EPS ($p=0.0011$).

Conclusion: This is the the largest cohort of NS patients systematically assessed for EPS. In comparison to MS, we find a statistically significant increased frequency of extrapyramidal signs in NS. This finding raises the question of the relation between NS and Parkinson's disease.

Disclosure: Nothing to disclose

P2176

Treatment efficiency of immunoglobulins and therapeutic plasma exchange in neurology

M. Fernandez-Fournier, A. Tallon, C. Calle De Miguel, J. Rodríguez-Pardo, I. Puertas Muñoz, F.J. Rodríguez de Rivera, E. Diez Tejedor
Hospital Universitario La Paz, Neurology, Madrid, Spain

Background and aims: Intravenous immunoglobulins (IVIG) and Therapeutic Plasma Exchange (TPE) are effective treatments for certain neuroimmunological diseases. Both are costly treatments administered in a hospital setting. According to current medical literature there are different degrees of evidence for each of these treatments depending on the disease. We aimed to determine the most efficient treatment option for neurological diseases.

Methods: 1. Clinical guideline revision to determine equivalent indications for IVIG and TPE in Neurlogy. 2. Cost studies to determine the cost of a standard session of IVIG and TPE, and the cost of hospital stay in a Neurology Department of a Spanish tertiary University Hospital. 3. Retrospective cost-benefit study of the use of IVIG and TPE between January 2008 and March 2014.

Results: IVIG and TPE use is equivalent in acute Myasthenia Gravis (aMG) and Guillain-Barré Syndrome (GBS). The cost of a treatment session of IVIG was 5,023.90€ and of 2,465.06€ for TPE. In the study period, 48 patients were hospitalized for aMG, 17 were treated with IVIG and 4 with TPE; and 39 patients were hospitalized for GBS, 28 were treated with IVIG and 41with TPE. Hospital stay was 9.5 days (±4.8) for aMG patients treated with en IVIG and 12.0 days (±6.9) for those treated with TPE, $p>0.05$.

Conclusion: For an equivalent indication, treatment with TPE entails a lower cost per process and is thus the most efficient treatment alternative.

Disclosure: Nothing to disclose

P2177

Immunohistochemical screening for auto-antibodies in recent onset type 1 narcolepsy and after H1N1 vaccination

A. van der Heide[1], I.M. Hegeman-Kleinn[1], E. Peeters[2], G.J. Lammers[1], R. Fronczek[1]
[1]*Leiden University Medical Centre, Neurology, Leiden, The Netherlands,* [2]*MCH Westeinde, Neurology, Den Haag, The Netherlands*

Background and aims: As a result of a selective loss of the hypocretin containing neurons in the hypothalamus, narcolepsy with cataplexy patients typically have undetectable hypocretin-1 levels in the CSF. Based on the tight HLA-DQB1*06:02 association, an autoimmune attack targeting hypothalamic hypocretin (orexin) neurons is hypothesised. So far, no direct evidence for an autoimmune attack was found. One of the major limitations of previous studies was that none included patients close to disease onset.

Methods: We screened serum of 21 narcolepsy type 1 patients (13 male, 8 female) close to disease onset (median duration of symptoms 11 months; range 2-48 months) for antibodies against hypocretin neurons using immunohistochemistry. In 17 patients hypocretin-1 was measured, all were hypocretin-1 deficient. 20 patients were HLA-typed and were positive for DQB1*06:02. Six patients were vaccinated against H1N1 before onset of narcoleptic symptoms. Positive controls were a patient and a control subject that have autoantibodies against hypocretin neurons; described in our previous study.

Results: No autoantibodies against hypocretin neurons could be detected, including the patients that were vaccinated against H1N1. The two positive controls were still positive.

Conclusion: No evidence was found for autoantibodies in serum of narcolepsy patients close to disease onset including patients vaccinated for H1N1. This finding not necessarily contradicts the autoimmune hypothesis, nor does it implicate an absence of autoantibodies at any time in the development of the disease. For future studies, it could be of interest to screen CSF of patients as close as possible to disease onset for autoantibodies, or focus more on T-cell immunology.

Disclosure: Nothing to disclose

P2178

The cytokine profile in CSF differentiates multifocal motor neuropathy from progressive muscular atrophy

T. Furukawa[1], N. Matsui[1], K. Fujita[1], H. Nodera[2], F. Shimizu[3], K. Miyamoto[4], Y. Takahashi[5], T. Kanda[6], S. Kusunoki[4], Y. Izumi[7], R. Kaji[7]

[1]Institute of Health Biosciences, Tokushima University, Tokushima, Japan, [2]Insitute of Health Bioscience, Tokushima University, Tokushima, Japan, [3]Yamaguchi University Graduate School of Medicine, Ube, Japan, [4]Kinki University School of Medicine, Osaka, Japan, [5]National Epilepsy Centor, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan, [6]Yamaguchi University Graduate School of medicine, Ube, Japan, [7]Institute of Health Bioscience, Tokushima University, Tokushima, Japan

Background and aims: Multifocal motor neuropathy (MMN) can occasionally mimic motor neuron disease, especially the lower motor neuron variant progressive muscular atrophy (PMA). We examined the cytokine and chemokine profiles of MMN in comparison with those with PMA and amyotrophic lateral sclerosis (ALS) to investigate the immunological differences in the CNS.

Methods: The CSF from 12 patients with MMN, 8 with PMA, 26 with sporadic ALS, and 10 with other non-inflammatory neurological disorders were analyzed for 27 cytokines and chemokines using multiplex bead array. The cytokine titers of the four groups were compared, and the correlations between the titers of relevant cytokines and clinical parameters were evaluated.

Results: There were no obvious intrathecal changes in MMN except for IL-1ra. In contrast, the titers of IL-7, IL-17, eotaxin/CCL11, FGF-2, G-CSF, and PDGF-BB were significantly elevated in both PMA and ALS. In ALS, IL-4 and Eotaxin/CCL11 titers were higher in the patients with slowly progressive course, and IL-10 titers were higher in those with milder stage of the disease.

Conclusion: The CSF cytokine profile of MMN is distinct from those of PMA and ALS. On the other hand, the similarity of cytokine profiles in PMA and ALS suggests that PMA, even without clinical evidence of upper motor neuron involvement, shares common immunological features with ALS in the CNS.

Disclosure: Supported by JSPS KAKENHI Grant-in-Aid for Young Scientists (B) 25870477; Grants-in-Aid from the Neuroimmunological Disease Research Committee and the Research Committee of CNS Degenerative Diseases, the Ministry of Health, Labor and Welfare of Japan.

P2179

A study of Guillain Barré syndrome in Malta

J. Gauci[1], M. Mifsud[2], M. Vella[2], M. Mallia[2]

[1]L-Msida MSD, Malta, [2]Department of Neurology, Msida, Malta

Background and aims: Since the near global eradication of poliomyelitis, Guillain-Barré syndrome (GBS) has become the commonest cause of acute neuromuscular paralysis. Despite available treatment, GBS still results in a significant amount of morbidity and mortality.

Our aim was to conduct a retrospective analysis of the epidemiology and management of GBS in Malta.

Methods: All cases of GBS presenting between 2002 and 2012 were identified through the Hospital Activity Analysis Register in Malta's only public tertiary hospital (St. Luke's / Mater Dei Hospital).

Results: A total of 53 patients were identified and studied. The incidence of GBS ranged from 0.25 to 3.58 per 100,000 per year. The peak incidence was in spring and autumn months. Contrary to available European data, 74% of nerve conduction studies were of axonal subtype, while only 15% were of demyelinating subtype. Typical albuminocytological dissociation in the cerebrospinal fluid was present in 62%. Lung function tests were performed in only 4%. 87% of patients were treated with intravenous immunoglobulins, while 9% also received plasma exchange. 28% of patients required ITU/HDU admission. Autonomic involvement and neuropathic pain were observed in 26% and 36% respectively. 74% of patients were discharged within 20 days; 17% of these were transferred to a rehabilitation hospital. We report a mortality rate of 0%.

Conclusion: This is the first national study on GBS. Most of our data is in concordance with international data, save for the predominance of the axonal subtype. This suggests the possibility of a specific aetiological agent with resultant cross-reactive antibody production and axonal damage.

Disclosure: Nothing to disclose

P2180

Depletion of CD11c positive dendritic cells is protective in a murine model of ischemic stroke

M. Gelderblom[1], P. Ludewig[1], P. Arunachalam[1], A. Planas[2], T. Magnus[3]

[1]University Hospital Hamburg-Eppendorf, Neurology, Hamburg, Germany, [2]IDIBAPS, Barcelona, Spain, [3]University Hospital Hamburg-Eppendorf, Hamburg, Germany

Background and aims: The devastating effect of ischemic stroke is attenuated in mice lacking conventional and unconventional T-cells, suggesting that inflammation enhances tissue damage in cerebral ischemia. Our goal was to explore the functional contribution of CD11c positive dendritic cells to the tissue damage following stroke

Methods: In accordance with current quality guidelines, we characterized dendritic cells in a murine ischemic stroke model. Depletion of CD11c positive dendritic cells was achieved in a transgenic mouse model in which the diphtheria toxin receptor is expressed under the CD11c promoter (CD11c.DTR).

Results: Depletion of dendritic cells in the CD11c.DTR resulted in significantly decreased infarct size. Mechanistically, depletion of CD11c positive dendritic cells was associated with an reduction of IL-17 in γδ T-cells.

Conclusion: We propose that dendritic cells contribute to the postischemic tissue damage by induction of detrimental IL-17 in atypical T-cells.

Disclosure: Dr. Gelderblom has received consulting fees from Merz pharmaceuticals and Allergan.

P2181

CX3CR1 signalling important in maintaining an immune barrier following S. aureus challenge in the compromised olfactory pathway

J. Harris

Hobart, Australia

Background and aims: Infection of the central nervous system causing encephalitis and meningitis via the olfactory pathway is relatively infrequent, suggesting the presence of effective endogenous innate defence mechanisms. This study investigates signaling between the neuroprotective chemokine CX3CL1 and its receptor CX3CR1 and regulation of both nitric oxide production and cytokine expression levels in response to bacteria in the compromised olfactory pathway.

Methods: The olfactory epithelium of wild type C57/BL6 and CX3CR1GFP/GFP mice was compromised using 1% TritonX-100 solution. Fluorescently labeled S. aureus were introduced into the nasal cavity and the expression of inducible nitric oxide synthase (iNOS) and GFP or Iba1 examined by immunofluorescence. Cytokine profiles and bacterial clearance were determined.

Results: CX3CR1 deficiency allowed increased numbers of bacteria to infiltrate the olfactory bulb. In CX3CR1 GFP/GFP mice numbers of iNOS-expressing cells were significantly reduced compared to WT mice. Macrophages were depleted by 50% in bacteria treated CX3CR1 GFP/GFP mice but were increased in WT mice. Following S. aureus exposure in WT mice expression of tumour necrosis factor-alpha and interleukin-6 increased within 48h and interleukin-10 and interleukin-1beta decreased. In contrast there were no changes in the cytokine profile of CX3CR1GFP/GFP mice.

Conclusion: The immune barrier was impaired in the CX3CR1GFP/GFP mice as shown by marked infiltration of S. aureus into the granule layer of the OB, reduced numbers of microglia and lack of cytokine and iNOS induction. Thus, CX3CR1/CX3CL1 signaling plays a key role in the innate immune response in the olfactory pathway.

Disclosure: Nothing to disclose

Neurological manifestations of systemic disease 1

P2182

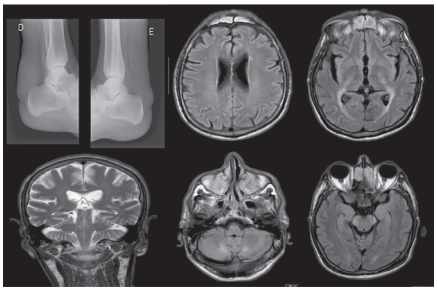
A case of Cerebrotendinous Xanthomatosis with two new heterozygous variants of the CYP27A1 gene

R. Araújo[1], P. Correia[1], A. Ribeiro[2]
[1]Centro Hospitalar e Universitário de Coimbra, Neurology, Coimbra, Portugal, [2]Hospital Garcia da Orta, Neurologia, Lisbon, Portugal

Background and aims: Cerebrotendinous xanthomatosis (CTX) is a rare metabolic disorder caused by a defective mitochondrial enzyme affecting bile acid synthesis and cholestanol production. Its clinical manifestations include cataracts, tendinous xanthomathosis and progressive neurological impairment. Diagnosis can be made biochemically (elevated serum cholestanol levels) and genetically (molecular defects in the sterol 27-hydroxylase gene). Early diagnosis is mandatory due to the availability of disease-modifying therapy that can halt disease progression.

Case Report: A 48-year-old male presents with progressive gait impairment and falls. His medical history included juvenile cataracts and a mild mental development delay. He had an elder brother that experienced sudden death at the age of 44 who "looked and walked the same"; his father died at age 61 of stroke, and his mother had an aterothrombotic stroke at the age of 65. On examination he displayed tendon xanthomata, bilateral limb ataxia, spastic paraparesis, mild cerebellar gait ataxia and reduced left arm swing with bradykinesia on motor tasks.

Tendon xanthomata



Cerebral MRI findings; Heel X-Ray

Results: His MRI showed diffuse symmetrical white matter periventricular and cerebellar lesions with cortical atrophy. His blood cholestanol levels were high (60.6mmol/L). A heterozygous c.1016C>T mutation of the CYP27A1 gene was detected as well as two new previously undescribed heterozygous variants - C.545T>C (p.lle182Thr) and c.563G>C (p.Arg188Pro). Bioinformatic analysis indicates that the latter likely bears pathogenicity. The diagnosis of CTX was made and he was started on atorvastatine and chenodeoxycholic acid.

Conclusion: We report a rare metabolic disease with a new compound heterozygous gene mutation. Prompt diagnosis is mandatory since treatment is available.

Disclosure: Nothing to disclose

P2183

Neurological manifestations of Behçet's disease: 161 cases in one Moroccan center

S. Aidi[1], M. Benabdeljlil[2], M. Rahmani[3], D. Sefiani[4], M. El Alaoui Faris[5]

[1]Hôpital des Spécialités, Mohamed V university, Department of Neurology A and Neuropsychology, Rabat, Morocco, [2]Hôpital des spécialités, Mohamed V university, department of neurology and Neuropsychology, Rabat, Morocco, [3]Hôpital des Spécialités, Mohamed V university, Neurology A and Neuropsychology, Rabat, Morocco, [4]Hôpital My Youssef, CHU Ibn Sina, Rabat, Morocco, [5]Hôpital des Spécialités, Mohamed V university, Department of Neurology and Neuropsychology, Rabat, Morocco

Background and aims: Behçet's disease (BD) is a chronic multisystemic inflammatory disease, predominant within the Mediterranean countries and characterized by oral, genital mucous ulcers and uveitis. Neurological involvement is one of the most serious complications of BD and represents a major cause of morbidity.

Methods: 161 Moroccan cases of neurobehçet disease (NBD) have been categorized into two main groups: "parenchymal" CNS involvement, which includes hemispheric, brain-stem, spinal, and multifocal presentations; and "non parenchymal" CNS involvement, which includes dural sinus thrombosis and arterial involvement.

Results: Parenchymal CNS pattern was observed in 74% of our cases with a predominance of symptoms related to brainstem involvement (30%) such ophthalmoparesis, bulbar and pseudobulbar palsy. Other symptoms have been present with varying frequencies: cerebellar signs (52%), headache (52%), psychiatric and cognitive symptoms (34%), sphincter disturbances (22%), epilepsy (9%). Some features are less common such as optic neuropathy (2%) or peripheral neuropathy (1%). Non-parenchymal form was noted in 26% of our series essentially represented by cerebral venous thrombosis (CVT). Only 4 of cases have cerebral arterial involvement, three with intracranial aneurysm. All patients have cerebral imaging. Magnetic resonance imaging showed a caracteristic lesion in one third of our patients, located at the mesodiencephalic junction and the pontobulbar region. Treatment was based on corticosteroids in the two categories. Long-term maintenance with immunosuppressive agents was administrated in patients with parenchymal CNS involvement and anticoagulants in case of CVT.

Conclusion: Neurological involvement represents a major complication of BD which requires early diagnosis and long term management.

Disclosure: Nothing to disclose

P2184

Anderson-Fabry disease and risk of misdiagnosis: an Italian family with late onset neurological manifestations.

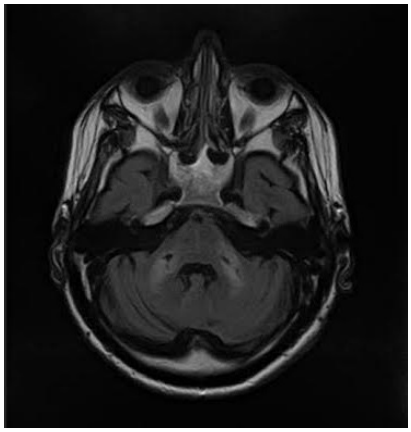
F. Corea[1], M. Barbi[2], P. Brustenghi[1], E. Todeschini[2], F. Crusco[3], G. Savarese[4], M. Zampolini[5]

[1]USL Umbria [2], Neurorahabilitation, Foligno, Italy, [2]USL Umbria [2], Neurorahabilitation, Trevi, Italy, [3]USL Umbria [2], Radiology, Foligno, Italy, [4]USL Umbria [2], Cardiology, Foligno, Italy, [5]USL Umbria [2], Neurorehabilitation, Foligno, Italy

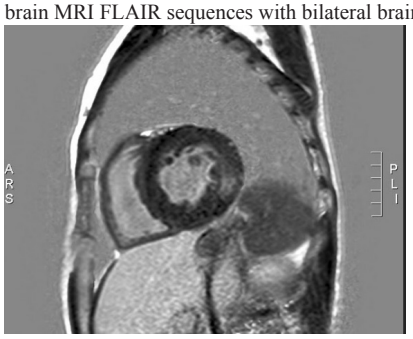
Background and aims: We describe two patients with isolated neurological manifestation from an Italian family later diagnosed with Anderson-Fabry disease. Clinical examination, neuroimaging (MRI), biochemical and genetic analyses were carried out in all the patients.

Case Report: Case 1: A male patient of 49 years with history of TIAs presented an ischemic vertebrobasilar stroke, retinopathy and cardiomiopathy A contrats enhanced MR cardiac imaging showed Left Ventricular Hypertrophy with patchy mid-wall abnormalities. Case 2: A female cousin, had diagnosis of probable primary progressive multiple sclerosis twenty years before at the age of 30, and treated with periodical steroideal infusions. Both had absence of alpha-galactosidase A activity detected by fluorimetric assay and genetic analysis by DNA sequencing demonstrated on exon 7 a mutation gor gene GLA c 1025G>A (p.R342Q).

Results: In both cases enzyme replacement therapy was recommended. MRI was abnormal in all the patients and showed lacunar infarctions in the periventricular white matter. In patients with Anderson-Fabry disease, stroke-like manifestations are frequent complications, and may be the first threatening clinical manifestation.



brain MRI FLAIR sequences with bilateral brain stem infarctions



CE cardiac MRI showing infero lateral enhancement

Conclusion: In young people with undefined stroke or neurological stroke-like conditions, even without signs of renal involvement, it is important to consider the diagnosis of Anderson-Fabry disease and so to perform clinical examination and biochemical analysis to avoid misdiagnosis.
Disclosure: Nothing to disclose

P2185

The correlation between the neurological complications of rheumatoid arthritis with the disease activity and functional impairment (disability)

M. Dafaalla[1], H. Eltoum[2], M.A. Taha[1], M.A. Abdelrahim[3], M.I. Alfaki[1], M. Alfaki[3], R.A. Alsherif[1], A.M. Hussein[4]
[1]Daoud Research Group, Khartoum, Sudan, [2]Omdurman university hospital., Department of rheumatology, , Khartoum, Sudan, [3]Daoud research group, Khartoum, Sudan, [4]Faculty of medicine, University of Khartoum, Department of Neurology, Khartoum, Sudan

Background and aims: To identify the impact and predictors of the neurological complications of rheumatoid arthritis (RA).
Methods: A case series study of 58 consecutive patients diagnosed as RA at Omdurman university hospital rheumatology clinic was done. Patients have another possible etiology for the neurological manifestations were excluded. The doctors of rheumatology clinic examined the patients and the Clinical Disease Activity Index (CDAI) was calculated. A senior consultant neurologist objectively assessed the neurological complications of RA. The patients were interviewed using the Health Assessment Questionnaire (HAQ) to evaluate the functional impairment. The rheumatoid factor status and the most recent ESR value were documented.
Results: 60.3% have neurological signs (pyramidal system signs 43.1%, extrapyramidal/cerebellar 0%, proximal weakness 8.6%, sensorimotor neuropathy 5.2%, pure sensory neuropathy 1.7%). The mean HAQ scores for patients who have neurological signs and those who do not 1.34 and 1.40 respectively without significant difference (P=0.778). The association between the neurological complications and disease activity, ESR value, and rheumatoid factor status is not significant (P=0.701, 0.515, 0.299 respectively). There is not only a strong association between the disease activity (CDAI) of RA and functional status (HAQ) of the patient (P=0.0, R=0.56), but also 30% of variability of the functional impairment can be attributed exclusively to the variability of the disease activity (R2=0.3).
Conclusion: The RA activity is the major determinant of disease morbidity. The functional impairment caused by the neurological complications of RA is negligible. The disease activity, ESR value, and rheumatoid factor status are poor predictors of the neurologic complications.
Disclosure: Nothing to disclose

P2186

Abstract cancelled

P2187

Clinico-radiological characteristics of primary and secondary neurological manifestations in a large cohort of HHT patients

M. Gallea[1], P. Favrole[1], M.F. Carette[2], S. Dupuis-Girod[3], S. Alamowitch[1]

[1]Hopital Saint Antoine, Neurology, Paris, France, [2]Hopital Tenon, Neurology, Paris, France, [3]Hopital Louis Pradel, Clinical Genetics, Lyons, France

Background and aims: Hereditary hemorrhagic telangiectasie (HHT) is an autosomal dominant genetic disease with vascular malformations, including pulmonary arteriovenous malformations (PAVMs), cerebral vascular malformations (CVMs). Main neurological complications are cerebral abscess and cerebral ischemic events (secondary neurological complications) and cerebral hemorrhages secondary to CVMs (primary neurological manifestations). Objective: To precisely describe primary and secondary neurological manifestations in a large cohort of consecutive patients with HHT and to evaluate gentype-phenotype correlations.

Methods: We performed a retrospective study of consecutive patients from 2 French HHT specialized centers. Inclusion criteria were: 1) a clinically definite diagnosis (Curacao criteria) and/or a genetically established diagnosis of HHT, and 2) a cerebral MRI and/or CT scan and with a MR and/or CT angiography. In these patients, we identified "neurological patients" if a neurological manifestation was reported and/or if a parenchymal and/or vascular lesion was reported on radiological explorations.

Results: 337 patients were included. 225 neurological patients were identified. The estimed prevalence of neurological complications is 10.1%. Primary neurological complications were reported in 113 patients (57% with Endogline mutation). Cerebral Arterio-veinous malformations (MAVc) were the most frequent of CVMs (26%). 14 patients patients had a symptomatic haemorrhage. Secondary neurological complications were present in 124 patients (35 with abscess and 100 with ischemic events), 73% with Endogline mutation. 86% of patient had PAMVs, frequently multiple and with an afferent artery diameter >3mm. The clinical prognosis was very good.

Conclusion: Neurological complications were not rare in HHT patients. Ischemic events were the most frequent et were associated with PAMVs. CMVs were predominantly silent.

Disclosure: Nothing to disclose

P2188

Severe cerebral involvement due to idiopathic systemic capillary leak syndrome

A.R. Günes, R. Weber, M. Krämer, P. Berlit

Alfried Krupp Krankenhaus, Department of Neurology, Essen, Germany

Background and aims: The idiopathic systemic capillary leak syndrome (SCLS) is a rare and life-threatening disorder, characterized by recurrent attacks of hypotension, hypalbuminemia and hemoconcentration. Cerebral involvement has been described in exceptional cases only.

Case Report: A 43-year-old woman presented with nausea, vomiting, confusion and expressive aphasia following gastrointestinal complaints of 2 days duration. Laboratory findings indicated hypoalbuminemia in the absence of albuminuria, hemoconcentration and a known monoclonal gammopathy. Serum electrolytes were normal. Lumbar puncture revealed normal CSF findings without cells, autoimmune antibodies or oligoclonal banding. The patient's clinical condition worsened with the development of generalized edemas and coma. The initial MRI showed contrast enhancement of the right temporal lobe (Figure 1) and the posterior part of the corpus callosum. Within 1 week after symptom onset MRI demonstrated symmetrical T2-lesions and diffusion restriction in the brainstem (Fig. 2), cerebellum, hippocampi, thalami and posterior part of the corpus callosum, respectively. We administered high-dose intravenous immunoglobulin (IVIG) and were able to extubate the awake patient. The patient's right hemiparesis and aphasia improved constantly and MRI findings were regressive (Fig. 3). With an IVIG prophylaxis every 4 weeks no more attacks occurred during follow up.

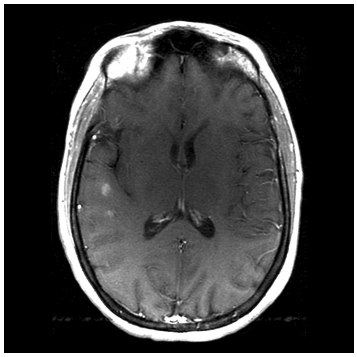


Figure 1

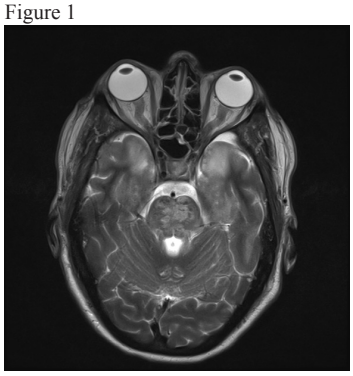


Figure 2

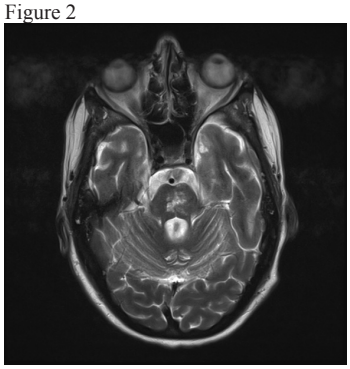


Figure 3

Conclusion: To our knowledge, this is the first case report describing massive bilateral cerebral involvement of SCLS. IVIG is a rational therapeutic option during the acute phase as well as for prophylaxis.
Disclosure: Nothing to disclose

P2189

Stroke induced by internal carotid artery dissection in a young patient with unknown cystathionine beta-synthase (CBS) deficiency

A. Lopez, N. Giraldo, J.J. Bravo, A. Parralo, C. Valencia, J.P. Cabello, A. Hernandez
Ciudad Real, Spain

Background and aims: Homocysteine is a sulfur-containing amino acid generated during methionine metabolism. It's known that hyperhomocysteinemia exerts toxic effects on endothelium and blood coagulation system. The most commonly involved enzyme in this process is CBS, which controls the transsulfuration of homocysteine to cystathione, and depends on vitamin B6 as a cofactor.
Commonly diagnosed during childhood, hyperhomocysteinemia is rarely uncovered in adults. We report a patient who presented a stroke due to an internal carotid occlusion. Etiological workup found CBS deficiency.
Case Report: A 35-year-old woman was admitted with right hemiparesis and mixed aphasia. Her only vascular risk factor was estroprogestative pill intake. Family medical history was unrevealing. Cranial Computed Tomography (CT) and Axial CT angiography confirmed a left internal carotid artery dissection, and ischemic stroke on the corresponding territory. (Img. 1 and 2)

Image1. Cranial TC.

Image2. Axial TC angyography.

Results: She was initially treated with aspirin, which was changed to acenocumarol after the acute stroke phase. Blood sampling found major hyperhomocysteinemia, with total plasma homocysteine >200μmol/l (normal <15μmol/l). Urinary amino acids chromatography confirmed high homocysteinuria and elevated methionin, compatible with CBS deficiency. Plasmatic folate, vitamin B 12, and cardiac studies were normal.
Vitamin supplementation and acenocumarol were maintained at the discharge. During subsequent weeks the condition steadily improved.
Conclusion: Plasma homocysteine has been investigated as an independent risk factor for ischaemic stroke. There is a recent suggestion that hyperhomocisteynemia may be associated with spontaneous cervical artery dissection. We aim to emphasize the importance of plasmatic homocistein study in both stroke and carotid disection, specially among young patients.
Disclosure: Nothing to disclose

Cerebrovascular diseases 4

P2201

Predicting poor functional outcome after acute ischemic supratentorial stroke using clinical parameters and parameters of quantitative electroencephalography

A. Kuznietsov, O. Kozyolkin
Zaporizhzhya State Medical University, Neurology, Zaporizhzhya, Ukraine

Background and aims: Elaboration of statistical models to predict functional recovery after acute ischemic supratentorial stroke (AISS) is a very important and relevant in modern angioneurology that can help the practicioners to improve treatment approaches. We therefore developed new model using clinical parameters and parameters of quantitative electroencephalography (QEEG).

Methods: 107 patients (mean age 67.9±0.8 years) were studied within first 72 hours after clinical onset of AISS. Clinical examination included evaluation by National Institute of Health Stroke Scale (NIHSS). Clinical and social outcome was defined by modified Rankin Scale (mRS) on 21st day from AISS onset. Poor functional outcome (PFO) was clarified in case of 4-5 score by mRS on 21th day. Separately to affected and intact hemisphere (IH) the values of absolute and relative spectrum rhythm power (RSRP), fronto-occipital gradients (FOG) of δ-, θ-, α-, β-ranges, θlo-, θhi-, αlo-, αhi-, βlo-, βhi-subranges were detected. Development of prognostic model was made by logistic regression and ROC-analysis.

Results: Out of 107 stroke patients, 48 (44.9%) had PFO. Near 60 models were obtained. The model with the largest area under the curve=0.999 was: β=3,195*(NIHSS score on the 3rd day)+0.228*(RSRP of δ-range in IH)–0.29*(RSRP of θlo-subrange in IH)-19.989*(FOG of θlo-subrange in IH)-34.879. Significance level of Hosmer-Lemeshow-test for selected model p=0.989, Percent Concordant=99.9. Optimal cut-off value of β, which predicted PFO with sensitivity=97.9% and specificity=98.3%, was determined.

Conclusion: Developed prognostic model might be a powerful tool for predicting PFO of AISS and improving effectiveness of treatment.

Disclosure: Nothing to disclose

P2202

Clinical and radiological implication of incidental cerebral aneurysm in patients with cerebral infarction

S.-B. Kwon[1], C.-Y. Lee[1], S.-S. Hong[2], Y.-K. Minn[1], S. Jung[1], S.-H. Hwang[1]
[1]Hallym University College of Medicine, Neurology, Seoul, Korea, Republic of, [2]SoonChunHyang University Hospital, Radiology, Seoul, Korea, Republic of

Background and aims: Asymptomatic intracranial aneurysms are frequently encountered among patients visiting neurology clinic. Since not every patient but those with cerebral infarction undergo MRI, a group of infarcted patient serves useful representative for incidental unruptured intracranial aneurysms (UIAs). Since rupture of asymptomatic aneurysm brings catastrophic consequences, stratification of patients according to the possibility of harboring UIA is important. The aim of this study is to analyze the clinical and radiological characteristics of patients diagnosed with UIA in order to wisely select patients who need imaging work up for aneurysm more strongly than others.

Methods: Consecutive adult (≥18 years old) patients diagnosed with cerebral infarction admitted to our clinic during a 17-month period from Jan 2013 through Jun 2014 were included. Based on MR angiography, we divided and analyzed patients into those with and without UIAs.

Results: Of 321 patients, there were significant differences in female sex (P=0.004), presence of concurrent cerebral stenosis (P=0.036) between groups with (20; 6.2%) and without (301; 93.8%) UIAs. Factors associated with aneurysm in cerebral infarction patients according to logistic regression analysis were female gender (OR 4.37, 95% CI 1.537 – 12.394, P=0.006), and cerebral arterial stenosis (OR 2.87, 95% CI 1.004 – 8.18, P=0.049).

Conclusion: Incidental unruptured intracranial aneurysms found in acute cerebral infarction patients show several peculiar characteristics or tendencies including female predominance and cerebral stenosis. When treating female patients diagnosed with cerebral arterial stenosis, more cautions need to be paid to look for coexisting intracranial aneurysm.

Disclosure: Nothing to disclose

P2203

High on-treatment platelet reactivity to acetylsalicylic acid used in the secondary prevention of stroke and its risk factors

B. Labuz-Roszak, K. Pierzchala
Medical University of Silesia in Katowice, Chair and Clinical Department of Neurology in Zabrze , Zabrze, Poland

Background and aims: The aim of the study was to evaluate the prevalence of high on-treatment platelet reactivity (HOPR) to acetylsalicylic acid (ASA), used for secondary prevention of stroke, and the assessment of risk factors associated with HOPR.

Materials and Methods: 215 patients after ischaemic stroke taking ASA at the dose of 75-150 mg and 46 healthy volunteers were enrolled in the study. Platelet function was assessed by impedance aggregometry method in the whole blood using a multi-channel platelet function analyzer (Multiplate®, Dynabyte).

Results: HOPR (defined as AUC≥300 for arachidonic acid as agonist) was present in 85 (39.5%) of examined patients. The following risk factors for HOPR were determined: ASA dose ≤100mg/daily, heart rate > 70 beats/min, taking nitrates, haematocrit >40%, platelet count >300x103, duration of diabetes mellitus (DM) >5 years. The degree of diabetes control did not significantly influence platelet function. Function of platelets in vitro was different in women and men after using other agonists than arachidonic acid. The probability of the critical event was higher but insignificantly for patients with HOPR.

Conclusion: The study confirmed the occurrence of HOPR in many patients taking ASA for secondary stroke prevention. Risk factors for HOPR in the examined group were as follows: low ASA dose, higher heart rate, usage of some drugs, higher haematocrit and platelet count, long DM duration. Sympathetic activity could influence reactivity of platelets in patients taking ASA. The laboratory HOPR established by impedance aggregometry increases the risk for clinical aspirin resistance.

Disclosure: Nothing to disclose

P2204

Infratentorial variant of posterior reversible encephalopathy syndrome complicated by bilateral ischemic stroke

F. Ladeira, A. Caetano, S. Calado, F. Sá
CHLO, Neurology, Lisbon, Portugal

Background and aims: Reversible posterior leukoencephalopathy syndrome (PRES) rarely presents with exclusive infratentorial involvement. We report a case complicated by bilateral lacunar infarcts involving the posterior circulation.

Case Report: A 53-year-old man was admitted to the emergency department with subacute complaints of weakness and incoordination of the left limbs, diplopia, gait disturbance, and mild headache. He had a history of hypertension and HCV infection. Examination showed high blood pressure (203/125mmHg), left hemiparesia with extensor plantar response and left limb cerebellar ataxia. His lab results showed a mild increase of C reactive protein (5.8 mg/L) and cryoglobulinemia. CSF examination revealed a protein increase (79 mg/dL) with elevation of albumin quotient. Citology and intratecal synthesis of immunoglobulin were negative. His CT scan was normal, but cerebral MRI showed hyperintense lesion in T2 and FLAIR, involving the pons, and cerebellar hemispheres with normal diffusion weighted imaging (DWI) and increased signal in apparent diffusion coefficient (ADC) map and bilateral thalamocapsular lesions with restricted diffusion in DWI suggesting acute ischemic lesions. MRI spectroscopy didn't show any changes compatible with neoplasm. The patient was treated with methylprednisolone pulse and antihypertensive agents. After 1 week he showed no sign of paresia or ataxia although he maintained the Babinsky sign. The MRI after 1 month revealed that the infratentorial lesion had subsided but the supratentorial lesions remained.

Conclusion: The MRI features of our patient were consistent with infratentorial variant of PRES. Hypertension and cryoglobulinemia may have contributed to its development. Although infrequent, ischemic stroke is a potential complication.

Disclosure: Nothing to disclose

P2205
Intraorbital fistula – a case report

E. Liaptsi[1], F. Pico[1], M. L. Chadenat[1], J.M. Baud[2], E. Houdart[3]
[1]Versailles Mignot Hospital, Neurology department and Stroke Center, Versailles, France, [2]Versailles Mignot Hospital, Angiology Department, Versailles, France, [3] Lariboisière Hospital, Neuroradiology Department, Paris, France

Background and aims: Arteriovenous fistulas (AVFs) of the cavernous sinus are high flow arteriovenous shunts, usually presented by a classical triad of symptoms (exophthalmos, diplopia, chemosis).

Case Report: A 77-year-old woman presented with ptosis, vertical diplopia and left retro orbital headaches.The neurological examination reveals an isolated partial third nerve palsy: ptosis and vertical palsy without chemosis.

Results: An orbital MRI showed a T2 hypo-intense signal without opthalmic vein dilatation and motivated the research of a dural fistula. The presence of an opthalmic vein AVF was confirmed by an orbital ultra sound. A diagnostic arteriography demonstrated a type IIa dural fistula of the cavernous sinus; drained to the left and right petrosal sinus, without drainage in the meningial veins. Three weeks later, a clinical aggravation marked by severe invalidating headaches, diplopia and trigeminal neuralgia motivated the performance of a therapeutic arteriography. During the procedure, we found a modification of the fistula which was now equally drained in the left superficial middle cerebral vein, with a subsequent elevated central neurological risk. Successful obliteration of the fistulous connection was achieved by endovascular treatment, with restoration of normal arterial and venous flows, regression of headaches but persistence of the partial third nerve palsy.

Conclusion: The interests of this case are: i) the clinical presentation of an intraorbital arteriovenous fistula without chemosis ii) The diagnostic value of orbital ultrasound examination whereas orbital MRI was not conclusive. In such patients early diagnosis and treatment may prevent the high hemorrhage risk consequent to a possible cortical venous drainage.

Disclosure: Nothing to disclose

P2206
Abstract cancelled

P2207
Abstract cancelled

P2208
Impact of the new ASCOD classification: shifting categories and reducing undetermined strokes

L. Pereira, M. Rodrigues
Hospital Garcia de Orta, Neurology, Almada, Portugal

Background and aims: A useful stroke etiology classification should not categorize many patients as undetermined. ASCOD updated ASCO with this purpose. We explored this potential advantage in shifting patients to higher grades of disease likelihood and reducing undetermined strokes.

Methods: In a hospital-based study, stroke patients were classified prospectively according to ASCO phenotyping before ASCOD was published. Afterwards cases were reclassified without new diagnostic workup. We present proportions and shifts between grades, and frequencies of undetermined causality (without grade 1-2 evidence in any category).

Results: We included 460 patients (64.3% male, median age 66), 20.9% thrombolysed. A1 went from 19.3% in ASCO to 22.0% in ASCOD. S categories' proportions didn't change significantly. C2 went from 1.5% to 5.2%. ASCO O1 comprised 5.0%, distributed to ASCOD O1 2.4% and D1 2.8%. Grade 9 proportions shifted from ASCO to ASCOD: A9 16.7% to 5.4%; S9 remained 0.2%; C9 5.4% to 5.0%; O9 remained similar (25.9%-24.8%); and D9 was 2.8%. Patients with undetermined etiology were 28.9% in ASCO and 26.5% in ASCOD (p=0.46). Important category shifts were in: atherothrombosis 3.8% A3 to A1, and 66.2% A9 to A0; small-vessel disease 38.3% S3 to S0; cardioembolism 4.6% C0, 6.1% C3 and 8.0% C9 to C2; and other etiologies O1 loses 52.2% of subjects to O0 due to new dissection category.

Conclusion: New ASCOD seems important in reclassifying atherosclerotic stenosis severity, restricting the spectrum of small-vessel disease, and categorising multiterritorial infarcts as cardioembolic. While in individual categories the rate of incomplete workup lowers, the global number of undetermined strokes didn't change significantly.

Disclosure: Nothing to disclose

P2209

Utility of serial Holter ECG to detect paroxysmal atrial fibrillation in embolic stroke of undertermined source

J. Perez Lucas, P. Martínez Sánchez, B.E. Sanz Cuesta, J. Rodríguez Pardo de Donlebún, J. Díaz De Terán, I. Illán Gala, C.A. Calle de Miguel, E.M. Alba Suarez, B. Fuentes, E. Diez Tejedor

Hospital Universitario La Paz, Neurology, Madrid, Spain

Background and aims: To assess the utility serial 24-hours ECG Holter Monitoring (24h-HM) for the diagnosis of paroxysmal atrial fibrillation (PAF) in patients with an embolic stroke/transient ischemic attack of undetermined source (ESUS).

Methods: Observational study of patients with ESUS admitted at a Stroke Center (2009-2013). A first 24h-HM was performed in all cases and, if it was negative, a second or even a third HM was performed. Variables analysed: demographic data, vascular risk factors (VRF), clinical data, presence of carotid plaques by duplex ultrasound, left atrial enlargement by echocardiography. Multivariate models were preformed to identify those factors associated with the PAF detection.

Results: A total of 507 patients were diagnosed with an ESUS, mean age 70.28 years old (SD 12.8), 58% of them male. Overall, serial 24hHM found PAF in 25% of the cases (130/513 patients). The first 24hHM detected PAF in 23.9% (121/507), the second in 10.3% (6/58) and the third in 50% (3/6) of patients. Results are shown in Figure 1. Multivariate analysis showed that, for the first 24hHM, older age (OR 1.033, CI 95% 1.013-1,054) and LA enlargement (OR 2.012; CI 95% 1.289-3.143) were the factors associated to the presence of AF. For the second and third 24hHM, the multivariate analysis showed that LA enlargement (OR 13.333; CI 95% 1.539-115.548) was the only factor related to the PAF diagnosis.

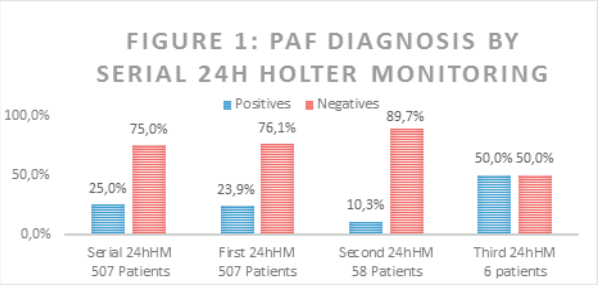


FIGURE 1: PAF diagnosis by serial 24h Holter monitoring

Conclusion: Serial 24hHM detect PAF in more than 25% of patients with ESUS. Age and left atrial enlargement are the factors more strongly associated with the PAF diagnosis.

Disclosure: Nothing to disclose

Clinical neurophysiology 1

P2210

A six-month registration of iatrogenic neuromuscular injuries in an EMG Unit

R. Arca[1], M. Morales[1], J. Baron Sanchez[2], C. Cabib[1], J. Valls-Solé[1]
[1]*Hospital Clinic Barcelona, Neurology, Barcelona, Spain,* [2]*Hospital Clinico de Valladolid, Neurology, Valladolid, Spain*

Background and aims: The usefulness of electrodiagnostic testing (EDX) is widely recognized in the assessment of neuromuscular injuries. It is often a resource for the assessment of iatrogenic neuromuscular injuries (INI). We evaluated the role of EMG examination in INI that came to our department between June and November 2014.

Methods or Materials or Case Report: We noted all INIs during six months routine EDX testing in our department. We revised patients' history to identify if INIs were fully recognized before the EDX examination and, in case of newly identified cases, whether the diagnosis prompted a change in patient's management.

Results: We identified 72 INI cases out of 654 studies (11%), 22 after chemotherapy, 32 after surgery, 9 after prolonged bed stay and 9 with other causes. In 10 cases (13.8%), no clinical suspicion of INI was found in patient's history. In 7 of these 10 patients and 22 others, the EDX had an influence on clinical management but this was not the case for patients submitted to chemotherapy. An improvement was seen in 37.5% of INI, 23 patients with focal nerve lesions (8 after prolonged bed stay, 15 for surgical procedures), 2 patients with polyneuropathy after toxicity and 2 patients with post-UCI neuromyopathy.

Conclusion: EDX may be useful in the diagnostic workup of potential INI. It is essential for diagnosis and evaluation of nerve recovery especially in focal lesions that, in our sample, have the higher rate of improvement. Although it does not change the management of patients submitted to chemotherapy, it helps with their monitoring.

Disclosure: Nothing to disclose

P2211

Effect of short-term vibration on cutaneous silent period

S. Aydın, Y. Bakuy, M. Kızıltan
Istanbul University, Cerrahpasa Medical Faculty, Neurology, istanbul, Turkey

Background and aims: Suppression of ongoing electromyography activation following cutaneous nerve stimulation is called cutaneous silent period (CuSP). CuSP is spinal inhibitory reflex mediated by small diameter fibers (A delta fibers) and large diameter fibers (alpha motor axons). The role of muscle spindles afferents had not been studied. We aimed to evaluate whether there is a contribution of these nerves during and after short–term vibration application.

Methods: The study group's age was between 29 and 44 (mean: 34.7±5.25), including healthy (6 male) volunteers. Right median nerve motor and sensory action potentials and CuSPs were recorded on abductor pollicis breves muscle by stimulation of median nerve of index finger before, during and after appliance of vibration. Vibration frequency was 100 Hz and 1mm of amplitude and was applied to forearm for 2 minutes. Data gained and rectified from the recordings of 10 volunteers were examined for their initial and endpoint latency periods, CuSP intervals, and suppression of EMGs.

Results: Average latency and duration of CuSP before, during and after vibration period were (14.80±77.6/ 40.1±10.84), (84.46±4.27/ 34.53±4.47) and (75.94±13.33/ 35.66±6.15) respectively. Although our results is not statistically significant, onset latency CuSP during vibration was prolonged, duration of CuSP was shortened.

Conclusion: Vibration is a potent stimulus for the primary muscle spindle endings and induce increased discharges of Ia afferents. Purpose of this study was to evaluate the contribution of la afferents on CuSP, however our results did not demonstrate a significant effect of vibration on CuSP activity.

Disclosure: Nothing to disclose

P2212

Slow right prefrontal repetitive transcranial magnetic stimulation for the treatment of resistant depressive symptoms in a progressive supranuclear palsy patient

S. Boulogne, F. Le Camus, R. Bation, F. Galvao, F. Haesebaert
Hopital Le Vinatier, Treatment-Resistant Depression Unit, Lyons, France

Background and aims: Repetitive Transcranial Magnetic Stimulation (rTMS) applied on Dorso Lateral Prefrontal Cortex (DLPFC) is increasingly used for treatment-resistant depression but has never been evaluated for depressive symptoms associated with neurodegenerative diseases.

Case Report: We report the case of a 62-year-old man diagnosed with progressive supranuclear palsy (PSP) presenting a severe comorbid depression. PSP began with insidious personality change associated with mood disturbance and anxiety; vertical ophtalmoplegia, axial rigidity and dysarthria added up progressively. Ten years after onset, he was admitted to our treatment-resistant depression unit for a melancholic depression, the Montgomery-Asberg Depression Rating scale (MADRS) was rated 33/60. Due to significant side effects and inefficiency of several antidepressant drugs, a rTMS therapy targeting the right DLPC was performed: 20 daily sessions of 360 stimulations at 1 Hz frequency and 120% resting motor threshold intensity. Psychiatric symptoms and global functioning were evaluated at baseline and after session 10 & 20 with the MADRS, the StateTrait Anxiety Inventory (STAI), the Lille Apathy Rating Scale (LARS) and the Global Assessment of Functioning (GAF) Scale.

Results: A significant clinical response was obtained within 20 sessions with sustained effect. MADRS decreased by 64% from 33/60 to 12/60, LARS by 180% from -10/36 to -28/36, STAI by 18% from 72/80 to 61/80. GAF scale increased by 75% from 40/100 to 70/100. No side effects were reported.

Conclusion: 1 Hz DLPFC rTMS is noninvasive and well tolerated and could be an interesting antidepressant therapy in parkinsonian syndromes. This first report in PSP has to be replicated in larger sample.

Disclosure: Nothing to disclose

P2213

Quantitative EEG in patients with Parkinson's disease (PD) with and without a Mild Cognitive Impairment (MCI) - a topographic analysis

M. Chaturvedi
Basel, Switzerland

Background and aims: We investigated how certain qEEG variables, particularly signal power in the alpha1 (8-10Hz) and theta (4-8Hz) bands differed for MCI (mild cognitive impairment) and Non-MCI Parkinson patients in the different

Methods: High-resolution 256-channel EEG were recorded in 43 PD patients (MCI/non-MCI: 18/25 | age: 68.1±7.9 | female/male: 16/27). Semi-automatic processing of the data was done to calculate the relative power in alpha1 and theta bands across the different regions of the brain, apart from the global relative power. Follow-up recordings at four weeks (4W) and six months (6M) were collected for 32 patients (MCI/non-MCI: 13/19). Permutation tests on t-statistics were carried out to correct for multiple comparisons and effect sizes were calculated. To test for the differences in different regions of the brain, t-tests were carried out for both groups of patients.

Results: An increase ($p=0.017$; ES=0.789) in the theta and a decrease ($p=0.042$; ES=0.782) in the alpha1 signal power were associated with MCI in PD patients. Temporal, Occipital and Frontal Right regions of the brain in Baseline study patients were seen to significantly differ between MCI and Non-MCI patients. The Occipital Left region was also found to differ between the two groups of patients at the Follow-up recordings (4W and 6M).

Conclusion: Alpha1 and theta signals can be associated with MCI in PD patients. The signal differences in the anatomical regions of the brain can be investigated further to be used for screening PD patients for early cognitive deficits.

Disclosure: Nothing to disclose

P2214

Deep repetitive transcranial magnetic stimulation with H-coil in Alzheimer's disease: a double-blind, placebo-controlled pilot study

E. Coppi[1], L. Ferrari[1], A. Nuara[1], R. Chieffo[1], E. Houdayer[1], M. Bianco[1], M.P. Bernasconi[1], M. Falautano[1], A. Zangen[2], G. Comi[1], G. Magnani[1], L. Leocani[1]

[1]Neurological Dept. & Experimental Neurophysiology Unit - Institute of Experimental Neurology (INSPE); University Hospital-IRCCS San Raffaele, Milan, Italy, Neurology Department, [2]Ben-Gurion University, Department of Life Sciences, Beer-Sheva, Israel

Background and aims: Repetitive transcranial magnetic stimulation (rTMS) applied with focal coils in Alzheimer's disease (AD) revealed positive effects on cognition. The H-coil is able to depolarize deeper and wider neuronal structures compared with focal coils. Our aim was to evaluate feasibility, safety and efficacy of excitatory rTMS with H-coil in AD.

Methods: 30 AD subjects (age 70.21±8.66; MMSE 17.31±5.77), randomized in real and sham group, underwent 12 rTMS sessions within 4 weeks, then a 4-week maintenance (1/week), over the fronto-parieto-temporal lobes (10Hz; 120%RMT). Neuropsychological assessment (Alzheimer's Disease Assessment Scale cognitive - ADAS-cog, Mini-Mental State Examination-MMSE, Beck Depression Inventory-II, Clinical Global Impression-Improvement, a word recognition task) were performed at baseline, 4 weeks from start of treatment (4w), end of treatment (8w), follow-up (8 weeks after 8w).

Results: No serious side effects were reported and no patient dropped due to side effects. Four subjects were excluded from the analyses (1 acute myocardial infarction in the sham group, 1 misdiagnosis, 2 missing data). Comparing percent ADAS-cog change at 4w with a null hypothesis of 0 change, only the real group significantly improved (-7.22±10.49 %, p=0.046). To achieve 3-4 points group difference change ADAS-cog with 80% power, we calculated a sample size 16-22 per arm.

Conclusion: Our preliminary findings suggest that rTMS with H-coil is a safe and feasible procedure in AD, with good patients' adherence. Our neuropsychological data will be used to plan phase II trials on a larger sample. Future studies should explore earlier disease phases and the combination with cognitive training.

Disclosure: Nothing to disclose

P2215

Sensitivity and predictive value of OCT and VEP in multiple sclerosis

G. Di Maggio

Milan, Italy

Background and aims: To evaluate the role of optical coherence tomography (OCT) and visual evoked potentials (VEPs) in detecting visual involvement and monitoring multiple sclerosis (MS).

Methods: To study 121 consecutive subjects with MS. Of 242 eyes, 166 had no previous history of optic neuritis (ON), 22 had a single recent ON episode (<3 months); 54 had chronic ON (at least 1 episode >3 months before). All patients underwent assessment of EDSS, OCT retinal nerve fiber layer (RNFL) thickness and VEP (checkerboard, size 15'). 77 subjects underwent a second EDSS (EDSS2) evaluation after a mean time of 1.94 (+0.69) years (median EDSS 2, range 0-7).

Results: In eyes with recent ON, the sensitivity of OCT was 38.9% with a higher sensitivity of VEP (77.3%; McNemar p<0.02). In eyes with chronic ON, no significant difference was found between OCT (68.5%) and VEP (81.5%) sensitivity. In asymptomatic eyes, VEPs had a higher sensitivity (31.7%) vs OCT (19.9%; p=0.005); VEP/OCT combined detected abnormalities in 39.2%. In follow up evaluation, in patients without previous ON, basal OCT alterations (1 eye per patient) were associated with disability after 2 years (Mann-Whitney p=0.013), differently from VEP.

Conclusion: The present findings confirm that VEPs are more sensitive than OCT early after acute optic neuritis and in asymptomatic eyes. In eyes without previous optic neuritis, basal asymptomatic OCT abnormalities was associated with disability development after 2 years.

Disclosure: Part of this work was financially supported by Merck Serono S.A., Geneva, Switzerland. Merck Serono is the biopharmaceutical division of Merck KGaA, Darmstadt, Germany.

P2216

Variation of median nerve latency after long lasting phalen maneuver

H.M. D'Onofrio
Buenos Aires, Argentina

Background and aims: Carpal Tunnel Syndrome (CTS) is usually associated with risk occupational factors such as repetitiveness of single actions, prolonged postures or forceful work involving the wrist, so either muscle imbalance or nerve compression may act as biomechanical forces with a different effect on healthy individuals (HI) compared with patients suffering entrapment nerve disorders. Phalen maneuver (PMT) is highly recommended to trigger CTS symptoms because it provokes a reduced median nerve (MN) intraneural blood flow lasting one minute. To address whether a five minutes lasting PMT (5mPM) triggers a more serious detrimental effect on MN latencies in CTS patients compared with responses found in HI, CTS patients and HI underwent to MN neuroconduction study.
Methods: CTS: 24 arms/ HI 20 arms. MN motor distal latency (MDL) and sensitive latency (SL) to I,II,III digit were analyzed at rest and after PM held for 5 minutes
Results: 5mPM increased MNMDL and MNSL, and reduced MN thenar amplitude response: HI DML mean increase 0.04ms/ mean amplitude reduction of 0.793 mv compared to 0.272ms and 8.3mv found in CTS ($p<0.05$). HI SL mean increase of 0,05 ms to II/III digit compared to 0.125 and 0.118 ms found on CTS ($p<0.05$)
Conclusion: 5mPM on CTS patients has shown a higher influence on MN latency values . These findings should be considered in CTS workers at risk activities to analyze the way they have to manage their usual exposure to long lasting biomechanical forces to avoid an increase on MN neuroconduction impairment.
Disclosure: Nothing to disclose

P2217

The effect of cerebellar degeneration on human sensori-motor plasticity

R. Dubbioso, F. Manganelli, A. Antenora, G. De Michele, A. Filla, L. Santoro
University of Naples "Federico II", Department of Neurosciences, Reproductive Sciences and Odontostomatology, University Federico II of Naples, Italy., Naples, Italy

Background and aims: Plasticity of the primary motor cortex (M1) has a critical role in motor control and learning. The cerebellum facilitates these functions using sensory feedback. We investigated how cerebellar degeneration influences the plasticity of the M1 by using PAS (paired associative plasticity) technique. PAS involves repeated pairs of electrical stimuli to the median nerve and transcranial magnetic stimulation (TMS) of the motor cortex. If the interval between peripheral and TMS stimulation is around 21–25ms, corticospinal excitability is increased via a long-term potentiation (LTP)-like effect within M1. Our aims were: (i) to explore the presence of a time-specific influence of cerebellar degeneration on human associative plasticity; (ii) to evaluate the role of somatosensory pathway on cerebellar modulation of sensory-motor plasticity.

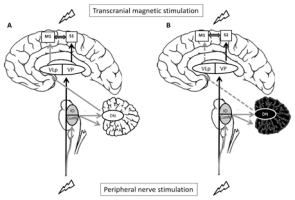


Figure 2 Schematic representation of the spino-cerebello-thalamo-cortical circuit models controlling the peripheral afferent information flow to motor cortex (M1). (A) Healthy subjects, (B) cerebellar patients. Afferent inputs are conveyed through infer

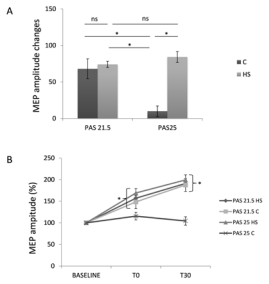


Figure 1 PAS 21.5 and 25 in healthy subjects (HS) and cerebellar patients (C) (A) Grand average of normalized MEPs at T0 and T30 to baseline in each session. Asterisks indicate significant differences from PAS 25 of cerebellar patients

Methods: We studied 10 patients with pure cerebellar atrophy and 10 age-matched healthy subjects. Motor-evoked-potentials amplitudes, short-afferent inhibition, motor thresholds, I/O curves, somatosensory-evoked-potentials (SEPs) were measured before, just after and 30 min after PAS at interstimulus-intervals of 21.5 and 25ms.
Results: In cerebellar patients LTP-like effect induced by PAS was abolished at 25 but not at 21.5ms (figure 1). SEPs showed that the amplitude of P25 wave was markedly reduced in patients with a more severe clinical and radiological impairment of cerebellum.
Conclusion: Cerebellar patients have an altered capability of cerebellar filtering or processing of time-specific incoming sensory volleys, influencing the plasticity of M1 (figure 2). These results have important implication for understanding the pathophysiology of neurological disorders in which cerebellar impairment is assumed.
Disclosure: Nothing to disclose

Ethics in neurology; History of Neurology; Neurology and Arts

P2218

The dementia of King Ferdinand VI of Spain.

S. Fernández Menéndez[1], N. González[1], L.B. Lara Lezama[2], R. Garcia Santiago[3], L. Redondo Robles[2], A. Álvarez Noval[4], B. Cabezas Delamare[2], A. Ares-Luque[2], J.M. González González[5]
[1]León, Spain, [2]Complejo Asistencial Universitario de Leon, Leon, Spain, [3]Leon, Spain, [4]complejo asistencial universitario de leon, leon, Spain, [5]autónomo, Oviedo, Spain

Background and aims: Ferdinand VI was king of Spain from 1746 until 1759. His last year of reign is known as "the year without a king" because the rapidly progressive deterioration of his mental health status. The clinical condition has been always attributed to a pure psychiatric disorder by historians.

Methods: We reviewed the primary and secondary sources of information, mainly the manuscript written by the principal physician of King Ferdinand VI, Andres Piquer y Arrufat. We made an evaluation of the clinical situation and we tried to find out the cause of the royal illness.

Results: Ferdinand VI had prior depressive episodes and the clinical deterioration of his last year started with the death of his beloved wife. At first, the symptoms were similar to the symptoms of a major depressive disorder, but the King had a rapidly progressive deterioration, with severe changes in personality and behavior. Later on, Ferdinand VI suffered seizures, myoclonus and fell into a state of prostration. He died 1 year after his clinical deterioration was marked, although it is probable that the first symptoms appeared before reported or they were attributed to his previous depressive episodes.

Conclusion: The cause of the illness of King Ferdinand VI will never be discovered. Although it is possible that it could have been a pure psychiatric disorder, there is enough information to think about a rapidly progressive dementia as the main cause of his clinical worsening and death.

Disclosure: Nothing to disclose

P2219

Neurosyphilis and classical music: the great composers and "The Great Imitator"

M. Kahakura Franco Pedro[1], F.M. Branco Germiniani[1], H.A. Ghizoni Teive[2]
[1]Curitiba, Brazil, [2]UFPR, Curitiba, Brazil

Background and aims: Neurosyphilis is one of the most devastating forms of the venereal disease; throughout history, many were victimized by it, including several classical composers, with a wide range of clinical presentations, whose cases we analysed.

Methods: Six articles with descriptions of composers with possible neurosyphilis were revised, as well as references in musicology.

Results: Usually a late manifestation of Treponema pallidum infection, neurosyphilis, whose manifestations include general paresis, tabes dorsalis and meningeal signs, among others, is a possible diagnosis for composers such as Beethoven, whose progressive hearing loss greatly influenced his career, culminating in complete deafness. In his autopsy cochlear nerve atrophy and cochlear inflammation were described - findings coherent with neurosyphilis. Donizetti, who was treated at the Salpêtrière, developed behavioral changes that ended his career, as well as headaches, general paresis and seizures. Both Schumann and Wolf suffered from personality changes, persecutory delusions and hallucinations; they developed delirium and died in poverty. Delius and Joplin also suffered from symptoms that can be attributed to syphilis. Autopsy findings confirmed the diagnosis of Smetana, who described in his diary symptoms of primary and secondary syphilis; dementia, deafness and auditory hallucinations with rapid progression. He developed tinnitus, which he represented musically in his First String Quartet.

Conclusion: Neurosyphilis victimized several notorious composers, often influencing their musical output. Although they may have had composed more pieces if it were not for the disease, it can be argued that neurosyphilis was a major source of inspiration as well, playing a pivotal role in the very genesis of musical masterpieces.

Disclosure: Nothing to disclose

P2220

Neurology in context of moral and political philosophy: support of UNO-agenda 21

E. Neu[1], M.C. Michailov[1], C. Lütge[1], R. Neu[1], M.-L. Gräfin von Brockdorff[1], B. Lichterman[2], G.-R. Stainov[3], T. Bilbili[1], G.-E. schulz[1], P. Birkenbihl[1], U. Welscher[1], M. Holler[4], M. Schratz[5], G. Weber[6]

[1]Inst. Eco-Med., [2]Inst. Eco-Med., Moscow, Russian Federation, [3]Inst. Eco-Med., Fulda, Germany, [4]Inst. Eco-Med., Hamburg, Germany, [5]Inst. Eco-Med., Innsbruck, Austria, [6]Inst. Eco-Med. (=Inst. Umweltmed.) c/o ICSD/Int. Acad. Sci., POB 340316, 80100 Muenchen, Germany (Berlin-Bratislava-Innsbruck-Muenchen-New Delhi-Paris-Sofia-Vienna), Vienna, Austria

Background and aims: Blood-circulation & neuroregulation from cellular upto system-levels have central position in all animal organisms: This way angio-cardiology & neurology are a-priori fundamental bio-medical disciplines, which have moral&scientific responsibility to support better health. This is also political obligation.

References: Michailov-Neu-Welscher et-al.: Philosophy: FISP (WorldCongrPhilos) 2013-Athens Congr.-Book 464-5&503-4&766; 2008-Seoul DVD2010 (ISBN-13:978-1-889680-835) Proc. Vol.4:101-108&Vol.20:203-214&Vol.37:195-202&Vol.45:229-237; 2003-Istanbul 279-280 Physiology: FEPS-2014-Budapest (FedEurPhysiolSci) Acta-Physiol 211:62-64 Psychology: IUPsyS-2012-Cape-Town PsycholPress/IntJPsychol 47/407.

Conception: In context of humanization, higher effectiveness (without stress) & internationalization of science&health-medicine has to be discussed: a. Integration of ethics/scientific-theory in neurological education&research. b. Foundation of elementary units for philosophical neurology to some clinics for neurology=CN. c. Foundation of national-European-international-CN via network of clinics from selected countries in context of creation of international universities proposed by Bertrand Russell (British Nobel-Laureate) & Gustav MENSCHING as paradigm for better education-research-technology. d. Implication of neurological topics to intern. congresses for philosophy-FISP, psychology-IUPsyS, physiology-IUPS, biophysics-IUPAB, chemistry-IUPAC, also in clinical-medicine (IUPHAR/FIGO/ISIM/SIU/etc). Fundamentals for a-d could be 1. Common educational/research programmes. 2. Common elementary administration & laboratories. 3. Recognition of participants as intern./continental professors/doctors, etc. 4. Possibility for regular work (not only guests) to institutes/branches in Africa-America-Asia-Australia-Europe. 5. Regular successive financial support for participants/projects by nat.-ministries/industry/Eur. Union/UNESCO,etc. 6. Possibility for whole-life-work after 60years as senior-scientists incl. honorary professors, institute-directors,etc

Conclusion: Implication of a-d&1-6 resp. in neurology will help UNO-Agenda21 by better health-education-therapy & prophylaxis in all countries. Social & political responsibility needs support of neurology-EAN incl. proposals a-d+1-6 by governments, foundations, EU/UNESCO/WHO.

Disclosure: Nothing to disclose

P2221

Functional lesional neurosurgery in the treatment of movement disorders: history and perspective

S. Schreglmann[1], R. Bauer[2], S. Hägele-Link[1], N. Wegener[1], E. Martin[3], G. Kägi[1]

[1]Kantonsspital St.Gallen, Department of Neurology, St.Gallen, Switzerland, [2]Kantonsspital St.Gallen, Department of Neurosurgery, St.Gallen, Switzerland, [3]University Children's Hospital Zurich, MR Centre , Zurich, Switzerland

Background and aims: Functional neurosurgery aims at changing the functionality of neuronal circuits involved e.g. in human motor control. Lesional treatment for movement disorders (MD) began in the mid 20th century and continuously evolved with the technology available. Its effects and side effects considerably advanced the understanding of basal ganglia function. We aim to trace major steps in the history of and perspectives for lesional treatment for MDs.

Methods: PubMed Literature review.

Results: From the first transventricular Caudate Nucleus resection, stereotaxy, chemopapillotomy, bipolar diathermy and radiofrequency ablation to the application of trajectory-free techniques such as GammaKnife and MR-guided focused high intensity ultrasound, surgical technology and technique evolved dramatically. Anatomically, procedures centered at the pallidum and only later included thalamic and subthalamic targets. Chronologically, the lesional treatment of MDs followed a bi-phasic pattern interrupted by the euphoric success of Levodopa treatment. Although interpretation of early literature results needs to take targeting precision, reporting bias and the lack of outcome scales into consideration, important lessons can be learned.

Table 1.: Chronological order of major clinical studies in the lesional neurosurgical treatment of movement disorders

Year	Author/Journal	Title
1940	Meyers HR.	Surgical procedure for postencephalitic tremor, with notes on the physiology of the premotor fibers.
1949	Oliver LC.	Surgery in Parkinson's disease. Division of the lateral pyramidal tract for tremor. Report on 48 operations.
1955	Cooper I.	Chemopallidotomy, an investigative technique in geriatric parkinsonians.
1958	Cooper IS, Bravo GI.	Chemopallidectomy and chemothalamectomy.
1960	Svennilson E, Torvik A, Lowe R, et al.	Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases.
1960	Hassler R, Riechert T, Mundinger F et al.	Physiological observations in stereotaxic operations in extrapyramidal motor disturbances.
1961	Mundinger F, Riechert T.	Long-term results of stereotactic treatment of extrapyramidal movement disorders
1964	Cooper IS.	Effect of thalamic lesions upon torticollis.
1972	Mundinger F, Riechert T, Disselhoff J.	Long- term results of stereotactic treatment of spasmodic torticollis.
1977	Goldhahn G, Goldhahn WE.	Experience with stereotaxic brain surgery for spasmodic torticollis
1983	Andrew J, Fowler CJ, Harrison JG.	Stereotaxic thalamotomy in 55 cases of dystonia.
1984	Narabayashi H, Yokochi F, Nakajima Y.	Levodopa-induced dyskinesia and thalamotomy.
1992	Laitinen LV, Bergenheim AT, Hariz MI.	Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease.
1993	Rand RW, Jacques DB, Melbye RW et al.	Gamma Knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results.
1995	Jankovic J, Cardoso F, Grossman RG, et al.	Outcome after stereotactic thalamotomy for parkinsonian, essential and other types of tremor.
1997	Lang AE, Lozano AM, Montgomery E et al.	Posteroventral medial pallidotomy in advanced Parkinson's disease.
2002	Alvarez L, Macias R, Lopez G, et al.	Bilateral dorsal subthalamotomy in Parkinson's disease (PD): initial response and evolution after 2 years.
2013	Lipsman N, Schwartz ML, Huang Y, et al.	MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept-study.
2013	Elias WJ, Huss D, Voss T et al.	A pilot study of focused ultrasound thalamotomy for essential tremor.

Table 1.: Chronological order of major clinical studies in the lesional neurosurgical treatment of movement disorders

Conclusion: In addition to deep brain stimulation (DBS), trajectory-free lesional approaches that spare the surrounding tissue by using focused thermal or radiation energy are a major addition to the neurosurgical armamentarium. When combined with advanced real-time image guidance and omitting radiation, such as in MR-guided focused high intensity ultrasound, new levels of targeting precision and safety seem achievable.

Disclosure: Nothing to disclose

P2222

Neuroanatomical and neuro-ophthalmological aspects in some works of Michelangelo

F. Thömke
Worms, Germany

Background and aims: Michelangelo's work as a sculptor and painter has attracted particular attention by physicians. Some noted deviations from normal anatomy such as the unnatural form of the left breast of the Notte in San Lorenzo's church (1), or blood filled veins in the sculpture of the dead Jesus in St. Peter (2). Others noted the lacking circumcision of David (3), or a multinodular goiter of the creator in the Separation of Light from Darkness in the Sistine Chapel (4).

Methods: Search for neurological and neuro-ophthalmological aspects in the works of Michealngelo.

Results: Previously, some authors thought that there is a hidden shape of the brain in the Creation of Adam (5), or the hidden shape of the brainstem in the Separation of Light from Darkness (6), or a horizontal eye deviation in the sculpture of David (7).

Own observations indicate a horizontal eye deviation in the Delphian Sybil, an ocular tilt reaction in the creator in The Creation of the Sun and Moon, and people with bilateral ptosis in the Last Judgement.

Conclusion: Any interpretation of art is exceedingly subjective and depends on the experiences and interests of the interpreter. Obviously, Michelangelo's work is of special interest for physicians to trace deviations from normal conditions and to speculate on their hidden meanings. This quest will continue.

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Disclosure: Nothing to disclose

P2223

An initial survey on neurological palliative care

L. Vanopdenbosch[1], D. Oliver[2]
[1]Bruges, Belgium, [2]Wisdom Hospice, Rochester, United Kingdom

Background and aims: Although the patients with progressive neurological disease may require palliative care there are often barriers between the specialties of neurology and palliative care in daily practice. To identify the barriers to overcome and close the gap between palliative care and neurology, we undertook a classical barriers analysis.

Methods: A cross sectional mixed methods study. Evident barriers were identified from a literature search and these were used to develop a semistructured interview. The interviews were undertaken with a representative sample of healthcare providers in neurology until there was topic saturation to identify emergent barriers. These barriers were quantified in a quantitative websurvey addressed to practising neurologists.

Results: We report the 50 initial replies of the first survey invitation to neurologists in Belgium. We found that moral, ethical, psychological or religious objections are not perceived as barriers for palliative care in neurology. A semantic barrier was identified: although much of the work of the neurologist can be classified as palliative care, neurologists would not use that term. There was disagreement whether time and money constraints pose a barrier. Intrinsic neurological aspects such as uncertain prognosis were seen as barriers. The greatest barrier for palliative care in neurology is lack of education and perceived lack of experience and exposure during training.

Conclusion: Moral, ethical, psychological, religious issues nor lack of time and funding seem to be the real reasons for the perceived lack of palliative care and neurology. We identified a semantic issue and an experience/education barrier.

Disclosure: Nothing to disclose

Headache and pain 3

P2224

Allodynia and medication-overuse headache in Portuguese migraineurs: An exploratory study

M. Mendonça, A. Caetano, M. Pinto, R. Miguel, R. Pelejão, R. Barbosa, F. Ladeira, F. Sá, M. Viana-Baptista
Centro Hospitalar de Lisboa Ocidental - Hospital Egas Moniz, Neurology Department, Lisbon, Portugal

Background and aims: A troubling aspect of migraine therapy is that overuse of acute headache medication can lead to medication-overuse headache (MOH). MOH pathophysiology remains largely unknown but some evidence suggests that it may be associated with central sensitization. Allodynia has been proposed as a manifestation of central sensitization so we assessed its presence in MOH patients.

Methods: 63 consecutive migraineurs were evaluated for the first-time. Demographic and diagnosis data was collected. Allodynia was assessed with 12-point Allodynia Symptom Checklist-12(ASC-12): No-to-mild-allodynia was defined as ASC-12 score 0-5 and moderate-to-severe-allodynia as score >5. Severe allodynia was defined as score ≥ 9. Hospital Anxiety and Depression Scale(HADS) was used. HADS and ASC-12 data was missing for one MOH and one non-MOH subject.

Results: 6 (6/63, 9.5%) of the patients fulfilled criteria for MOH and, when compared to non-MOH migraineurs, had a non-significantly higher age (41.5 versus 35.4 years), BMI (27.9 versus 24.5kg/m^2), headache intensity (10 versus 8) or HADS score(15 versus 14.4). Severe allodynia was present in all (5/5) MOH subjects and in 25.0% (14/56) of non-MOH (p=0.002; Fisher's exact test). Lowering cut-off, moderate-to-severe-allodynia was present in 46.4% (26/56) of non-MOH (p=0.053; Fisher's exact test).

Conclusion: Allodynia is common in MOH. This exploratory study supports the idea that central sensitization could be involved in MOH. Recommendations suggest withdrawal of the abused drugs and management of withdrawal headache. Acting on sensitization process could be helpful in the withdrawal. Future longitudinal studies are necessary to understand the relevance of addressing allodynia in MOH pathophysiology and treatment.

Disclosure: Nothing to disclose

P2225

Resting state functional connectivity abnormalities in pediatric patients with migraine

R. Messina[1], M.A. Rocca[1], B. Colombo[2], E. De Meo[1], A. Falini[3], G. Comi[2], M. Filippi[1]
[1]*San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy,* [2]*San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy,* [3]*Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy*

Background and aims: Aim of this study was to explore abnormalities of resting state (RS) functional connectivity (FC) and functional interaction among networks in pediatric patients with migraine.

Methods: Using a 3.0 Tesla scanner, RS functional magnetic resonance imaging scans were acquired from 13 pediatric migraine patients and 15 age-matched controls. Independent component analysis and a template-matching procedure were used to identify the default mode (DMN), salience (SN), fronto-parietal attention (FPN), working memory (WMN), sensorimotor (SM), auditory and visual (VN) networks. Within-group and between-group RS FC comparisons were performed using SPM8. The FNC toolbox was used to assess changes of interactions among RS networks. Correlations between RS FC abnormalities and patients' clinical characteristics were also assessed.

Results: Compared to controls, pediatric migraine patients had an increased RS FC of the precuneus of the DMN and the dorsolateral prefrontal cortex of the right WMN. They also experienced a decreased RS FC of the anterior cingulum of the SN and the temporo-parietal junction of the left WMN. FNC analysis detected a decreased FC between the DMN and right WMN, and an increased FC between the VN and FPN in migraine patients compared to controls. No significant correlation was found between intra- and inter-network RS FC abnormalities and patients's clinical characteristics.

Conclusion: Significant RS FC abnormalities occur in pain-processing networks of pediatric migraine patients. Brain regions involved in cognition were selectively involved, suggesting that abnormalities of cognitive modulation of pain in migraine patients occur from an early stage of the disease.

Disclosure: Nothing to disclose

P2226

Modulatory effect of L-kynurenine and probenecid on the trigeminal activation and sensitization in the rat

G. Nagy-Grócz[1], A. Fejes-Szabó[1], Z. Bohar[2], L. Tar[3], L. Vécsei[2], Á. Párdutz[1]

[1]University of Szeged, Department of Neurology, Szeged, Hungary, [2]University of Szeged, MTA-SZTE Neuroscience Research Group, Szeged, Hungary, [3]University of Szeged, Department of Neurology, Ulm, Germany

Background and aims: Migraine is one of the commonest neurological diseases, affecting 16% of the population. Despite intensive research, the exact pathomechanism of migraine is not fully understood, but the role of glutamate seems pivotal. Kynurenic acid (KYNA) is an endogenous antagonist of glutamate and α-7-nicotinic acethylcholine receptors. KYNA level in the central nervous system can be significantly increased by the administration of its precursor L-kynurenine (L-KYN) and the probenecid (PROB) an inhibitor of organic acid transporter. One of the animal models of trigeminal activation is the orofacial formalin test, which leads to activation and sensitization of the trigeminal system. We examined the effects of combined pretreatment of L-KYN and PROB on the formalin-induced changes in the second-order neurons in the trigeminal nucleus caudalis (TNC) of the rat.

Methods: Half of the animals received intraperitoneal L-KYN+PROB injection, the remaining rats got the placebo. One hour later animals received formalin in the right upper lip. Four hours later the animals were perfused transcardially and the TNC was removed for immunohistochemistry.

Results: Four hours after the formalin injection of rats, the number of c-Fos immunoreactive and calcium/calmodulin-dependent protein kinase II-alpha-immunoreactive neurons in the TNC was increased which reflect activation and sensitization of the trigeminal system respectively. The pretreatment with the combination of L-KYN and PROB significantly attenuated the formalin-induced changes in the TNC.

Conclusion: The manipulation of KYNA influences the activation and sensitization of the trigeminal system possibly via glutamate and α-7-nicotinic acethylcholine receptors presenting a possible new target for future antinociceptive agents.

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P2227

Spontaneous intracranial hypotension: definition of the serious form based on a series of 24 cases

S. Richard[1], A. Lyoubi Idrissi[1], G. Mione[1], A.M. Enea[1], E. Schmitt[2], O. Klein[3], X. Ducrocq[1]

[1]CHU Nancy, Neurology, Nancy, France, [2]CHU Nancy, Neuroradiology, Nancy, France, [3]CHU Nancy, Neurosurgery, Nancy, France

Background and aims: Recommended treatments for spontaneous intracranial hypotension (SIH) range from bed rest only for simple cases to neurosurgery for more serious forms. However, the serious form of SIH is poorly defined. A better description of the characteristics of patients with the serious form and their outcome may help define therapeutic options.

Methods: We reviewed 24 cases of patients with SIH and separated them into two groups according to whether or not they presented with signs of severity at admission: disturbance of consciousness, subdural hematomas and cerebral venous thrombosis (CVT).

Results: 9 patients (37%) were classified as having a serious form of SIH: 6 (25%) presented subdural hematomas; 3 (12%) disturbance of consciousness; and 1 (4%) CVT. Bed rest and epidural blood patches (EBP) were sufficient to treat all patients in the non-serious form group and four patients in the serious form group. 2 patients (8%) had to undergo cerebrospinal fluid leak repair, and 3 others (12%) evacuation of subdural hematomas. Time to diagnosis was longer in the serious form group (63 vs. 36 days). Outcome was good in both groups, with only one (4%) death due to extensive subdural hematomas. Time to recovery was higher in the serious form group (9 months vs. 4.8 months).

	Non-serious form group	Serious form group
Patients	15	9
Mean age, [range] (years)	44 [25-59]	49 [35-70]
Mean time to diagnosis, [range] (days)	36 [4-150]	63 [14-150]
Mean time to first epidural blood patch, [range] (days)	38 [17-100]	94[17-180]
Mean time to complete or near complete recovery, [range] (months)	4.8 [1-11]	9 [1-18]
Death or disability	0	1
Identified cerebrospinal fluid leak	3	3
Signs of severity		
Altered level of consciousness	N/A	3
Subdural hematoma	N/A	6
Cerebral venous thrombosis	N/A	1
Treatment		
Bed rest only	8	2
One epidural blood patch	4	1
Several epidural blood patches	3	5
Bed rest +/- epidural blood patch(es) only	15	4
Surgical repair of cerebrospinal fluid leak	0	2
Surgical evacuation of subdural hematoma	0	3

Table: Patients' characteristics, treatment and outcome of both groups: with and without sign of severity. N/A: Not applicable

Conclusion: The presence of subdural hematomas, disturbance of consciousness and a longer time to diagnosis and recovery seem to define the serious form of SIH. These patients may require neurosurgery, only after failure of conservative measures – bed rest and time – and EBP, with good outcome.
Disclosure: Nothing to disclose

P2228

Cost-effectiveness of self-management education versus usual care for patients with migraine headache: a pilot randomized controlled trial

L. Ridsdale[1], B. Osumili[2], P. McCrone[3]
[1]King's College London, Institute of Psychiatry, Psychology & Neuroscience, Basic and Clinical Neuroscience, London, United Kingdom, [2]King's College London, Institute of Psychiatry, Psychology & Neuroscience, Psychological Medicine, London, United Kingdom, [3]King's College London, Institute of Psychiatry, Psychology & Neuroscience, Health Services & Population Research, London, United Kingdom

Background: Headache is one of the common health conditions affecting society. In the context of high costs to patients, the health care system and society, the need for providing cost-effective care is apparent.
Aim To estimate the service and social costs of people with headache, and to compare the cost-effectiveness of participants randomised to receive minimal contact cognitive behaviour therapy (CBT) and relaxation with those receiving standard medical care (SMC) alone.
Methods: Participants recruited from specialist headache clinics across London were randomised to receive CBT and relaxation (plus SMC) or SMC alone. Service use over a four month period before and after randomisation was measured and lost employment recorded. These data were used to estimate economic costs. Predictors of cost were identified using regression and cost-effectiveness was compared by combining the costs with QALYs.
Results: The mean service and total costs were £858 and £6588 respectively. Service costs were significantly related to the number of days spent with headache and total costs were significantly related to the impact of headache. In the cost-effectiveness analysis, the ICER was £39,492 from the health care perspective. From the societal perspective, the intervention was dominant with 55.2% chance that it will results in lower costs and better outcomes at cost-effectiveness threshold of £20,000 per QALY.
Conclusion: Costs of headache are high and associated with severity. The intervention was not cost-effective from a healthcare perspective but was from a societal one.
Disclosure: Nothing to disclose

P2229

"MyMigraines" community: improving communication between migraine patient and neurologist

Á.L. Guerrero Peral[1], M. Ruiz Piñero[2], J.R. Miralles[3]
[1]Clinical Universitary Hospital in Valladolid, Neurology, Valladolid, Spain, [2]Valladolid, Spain, [3]Labs Health Company, Vigo, Spain

Background and aims: Using of a diary is invaluable in the adjustment of therapeutic strategy in a migraine patient. Diaries or calendars are useful tools to identify pain characteristics, possible trigger factors, and the amount of symptomatic drugs needed. Electronic diaries are available at many websites. "MyMigraines" is an app designed as a headache diary available for mobile devices.
Methods: "MyMigraines" allows migraine patients to collect in an easy and intuitive way, and using their own mobile devices, detailed information on their headache. Quality, intensity, location, duration and accompanying symptoms of headache episodes and their precipitating factors are so recorded. Symptomatic drugs used, and impact on daily living, including a possible visit to an emergency room are also collected. All this information is displayed in calendars.
Results: Migraine patients can also be invited by their neurologists to join "MyMigraines" community. "MyMigrainesPRO" is an app complementary to "MyMigraines" that allows doctors to check, using their own mobile devices, the evolution of each of their patients. Furthermore, the neurologists can activate an alert system individualized for each patient in order to be aware of certain clinical settings which may require therapeutic changes. "MyMigrainesPRO" also allows doctors to send messages to their patients in order to suggest specific behaviors or set a new medical visit.
Conclusion: Mobile technologies, along with its ecosystem of apps as "MyMigraines" community, have created a new model for health care. "Mymigraines" and "MyMigrainesPRO" allows migraine patients and neurologists, through their mobile devices, to improve their communication achieving a personalized therapy.
Disclosure: Nothing to disclose

P2230

Modulation of pain through cardio-visual stimulation in CRPS patients

M. Solcà[1], R. Ronchi[1], J. Bello Ruiz[1], T. Schmidlin[2], J.-Y. Beaulieu[3], F. Luthi[4], A. Schnider[5], A. Guggisberg[5], O. Blanke[1]

[1]Ecole Polytechnique Fédérale de Lausanne, Laboratory of Cognitive Neuroscience, Brain Mind Institute, School of Life Sciences,, Lausanne, Switzerland, [2]Ecole Polytechnique Fédérale de Lausanne, Center for Neuroprosthetics, Lausanne, Switzerland, [3]University Hospitals of Geneva, Service of Orthopedic Surgery, Unit of Hand Surgery, Geneva, Switzerland, [4]Clinique romande de réadaptation suvacare, Department for Musculoskeletal Rehabilitation, Sion, Switzerland, [5]University Hospital Geneva, Department of Clinical Neurosciences, Geneva, Switzerland

Background and aims: Complex regional pain syndrome (CRPS) is a painful condition that remains poorly understood and difficult to treat. Pain perception in healthy subjects has been found to be modulated by experimental manipulations of body ownership – leading to the experience of an artificial body or body part as belonging to their own body. Here we propose to use a similar illusion of bodily self-consciousness to relieve symptoms of CRPS.

Methods: 9 patients with CRPS following upper limb trauma were tested. We used virtual reality to expose patients to a "cardio-visual hand illusion", in which we presented to the participants a virtual hand flashing in synchrony (or in asynchrony in the control condition) with their own heartbeat. Participants underwent both synchronous and asynchronous conditions in a randomized order. Just before and after each condition, pain and grip strength were assessed using a visual analog scale (VAS) and a dynamometer, respectively.

Results: Preliminary results demonstrated a tendency towards a statistically significant reduction of pain perception selectively after exposure to the synchronous vs. asynchronous condition. Moreover, grip strength increased after exposure to the synchronous condition but reduced after the asynchronous condition probably through the analgesic effect.

Conclusion: This study provides preliminary evidence that the exposure to a virtual hand illusion based on cardio-visual integration can be used to treat CRPS symptoms. These findings could potentially lead to new non-invasive, analgesic rehabilitation approach for different pain conditions.

Disclosure: Nothing to disclose

Infection and AIDS 2

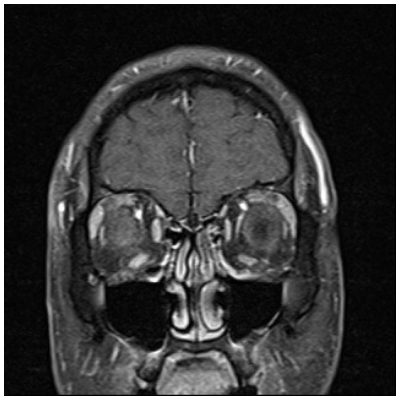
P2231

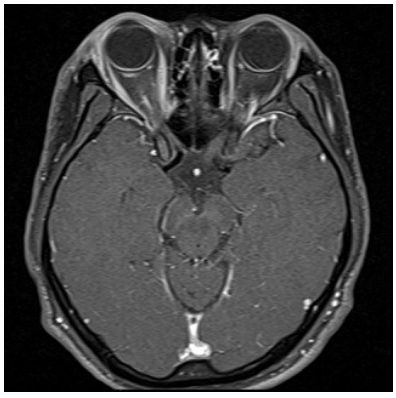
An unusual presentation of herpes zoster ophthalmicus: unilateral ophthalmoplegia caused by orbital myositis

S.-R. Kim
DONG-GANG general hospital, Neurology, ULSAN, Korea, Republic of

Background and aims: We present a case of unilateral ophthalmoplegia caused by orbital myositis associated with herpes zoster ophthalmicus (HZO) preceding vesicular eruptions.

Case Report: A 31-year-old man was admitted to our hospital with right ocular pain, proptosis, double vision, and a dull ahcy forehead pain on eye movement. One day later, he had a vesicular cutaneous rash in the distribution of the ophthalmic division of the right trigeminal nerve. Brain MRI revealed proptosis and swelling of right extraocular muscles. At that time, the level of creatinin phosphokinase was elevated.





Results: Treatment with antiviral agents and prednisolone resulted in a rapid improvement of the ophthalmoplegia.

Conclusion: HZO represents approximately 10 to 25 percent of all case of herpes zoster. Several complications associated with HZO commonly include keratoconjunctivitis, scleritis, uveitis, secondary glaucoma, chronic postherpetic neuralgia, and ophthalmoplegia caused by cranial nerve III, IV, or VI palsies. Ophthalmoplegia associated with HZO is not uncommon. The majority were due to involvement of ocular cranial nerve. We suppose that the pathogenensis of extraocular myositis in this patient may be caused by direct affection of herpes zoster virus. So, orbital manifestation preceded the skin lesion, extraocular muscle palsies recovered completely, and postherpetic neuralgia did not develop. HZO can present as unilateral myositis of the extraocular muscles with signs and symptoms of ophthalmoplegia, which are preceded by eruption of the classical skin rash. We have to consider the possibility of HZO in a patient of unilateral ophthalmoplegia in association with ipsilateral facial pain, even without skin rashes.

Disclosure: Nothing to disclose

P2232

Acute myeloneuropathies as a result of Ebola virus infection

D. Labunskiy[1], T. Fedotova[2], V. Poleshchuk[3]
[1]Santa Rosa CA, USA, [2]Tver State Medical Academy, Tver, Russian Federation, [3]Research Center of Neurology, Moscow, Russian Federation

Background and aims: Hemorrhagic fevers caused by Ebola virus are febrile illnesses with abnormal vascular regulation and vascular damage.The disease begins with severe weakness, headache, muscle aches, diarrhea, abdominal pain, sore throat. Macrophages participation in viral infections is widely reported. Microglial response and CNS involvement are also evident since syndrome, characterized by recurrent optic neuritis, cervical myelopathy from syringomyelia, paraparesis, amenorrhea-galactorrhea, and have other endocrine problems, has been described. Later, a dry cough and stabbing pains in the chest appears, developing signs of dehydration, vomiting, rash (about 50% of the patients), together with a decrease of liver and kidneys function.

Methods or Materials or Case Report: Pro-inflammatory cytokines, IFN-γ, IL-10, IL-12-p70, IL-1, IL-8, TNF-α, and IL-6 were measured simultaneously in tissue culture supernatants from primary brain derived macrophages, microglia, harvested from the brain tissue of 3 Ebola infected and deceased patients. We tested the effects of RAL on markers of astrocytosis and neurite integrity in primary human neuroglial cultures.

Results: It was revealed reliable decrease of IFN-γ, IL-10, IL-12-p70 in macrophages. The levels of IL-8, TNF-α, and IL-6 were increase in microglial cells of Ebola patiens in comparison with these parameters in patients died from other diseases.

Conclusion: Cell culture obtained from patients infected with Ebola virus and demonstrated before their death symptoms of typically myeloneuropathy: difficulty walking (gait difficulty) caused by sensory ataxia (irregular muscle coordination) due to dorsal column dysfunction or degeneration of the spinal cord, showed different pattern of cytokines change. Probably, these findings will contribute to more profound pathogenesis understanding of Ebola viral myeloneuropathy.

Disclosure: Nothing to disclose

P2233

Intramedullary abscess; an epidemiological and clinical analysis

C. Legault[1], S. Lapointe[2], R. Altman[3], D. Vinh[4]
[1]Montreal, Canada, [2]Université de Montréal, Neurology, Montreal, Canada, [3]McGill University, Neurology, Montreal, Canada, [4]McGill University, Microbiology and Infectious diseases, Montreal, Canada

Background and aims: Spinal cord abscess is a potentially devastating infection of the central nervous system. However, little is known about this entity. We characterize clinical, epidemiological and imaging features of spinal cord abscesses.

Methods: We performed a comprehensive literature review of reported intramedullary abscess and report a case of abscess due to Nocardia. Data were identified by searches of papers published on Embase, Medline, Cinahl and EMB databases, spanning the years 1830 – 2014, using key words "spinal cord", "intramedullary", "abscesses", "infection". An "abscess" had to be confirmed by imaging, culture from pyogenic debris/cerebrospinal fluid or intraoperatively.

Results: We identified 197 cases of intramedullary abscess. We found a striking male predominance (71%). Almost half (44%) had acute presentations (0-7 days). Most common risk factors were dermal sinuses (30%; 54% under 12 yo), concomitant systemic infection (31%) and immunocompromised states (13%). The most common microorganisms were Staphyloccocus and Streptococcus, followed by polymicrobial infections and Mycobacterium Tuberculosis. On imaging, the majority of abscesses showed multiple spinal segments extension (90%), gadolinium ring enhancement (68)%, and diffusion restriction (100%; n=3). CSF analysis was characterized by leukocytosis, proteinorachia (79%) and hypoglychoracchia (64%). Most patients were treated by tandem surgery and antibiotics (63%). Of the 107 outcomes reported, 30% fully recovered and 4% died during course of illness.

IMAGE 1: MRI at presentation

a) Axial T2

b) Axial T1/Gado

Nocardia intramedullary abscess case - Cervical MRI with T2 and Gadolinium

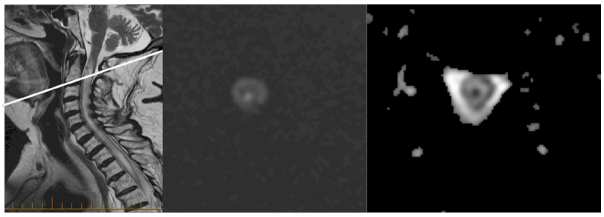
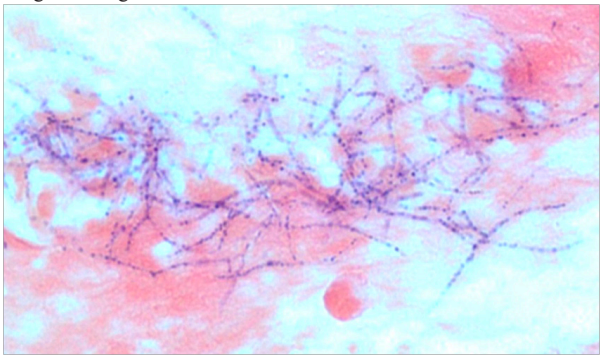


IMAGE 2: DWI and ADC of Medullary lesion

Nocardia intramedullary abscess case - Cervical MRI Diffusion weighted image



Norcardia intramedullary abscess - Direct modified Acid fast stain from pus drained from the lesion showing Nocardia farcinica colonies

Conclusion: Intramedullary abscesses are rare and associated with poor outcomes. Rapid diagnosis is paramount to minimize morbidity. Clues to diagnosis include predisposed host, pyogenic CSF, and gadolinium ring enhancement with diffusion restriction. Optimal treatment remains undefined, however combined surgical drainage with appropriate antimicrobials appears most successful.

Disclosure: Nothing to disclose

P2234

An outstanding and striking case of solitary cerebral toxoplasmosis mimicking glioblastoma as the first presentation of HIV

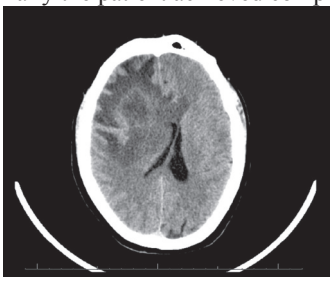
M. León Ruiz[1], M. Alonso Riaño[2], P. Gómez Iglesias[3], S. Delis Gómez[4], S. del Carmen Martínez[5], J. Benito-León[4], M.Á. García Soldevilla[1], L. Izquierdo Esteban[1], F. Cabrera Valdivia[1], J. Tejeiro Martínez[1], C.S. Abdelnour Ruiz[1], M. Molina Sánchez[1], M.H. Torregrosa Martínez[1], P. Hernández Navarro[1], E. García-Albea Ristol[1], O. Toldos González[2], A. Hernández Laín[2]

[1]Hospital Universitario Príncipe de Asturias, Neurology, Madrid, Spain, [2]Hospital Universitario 12 de Octubre, Pathology, Madrid, Spain, [3]Hospital Universitario Fundación Alcorcón, Pathology, Madrid, Spain, [4]Hospital Universitario 12 de Octubre, Neurology, Madrid, Spain, [5]Hospital Clínico Universitario de Salamanca, Pathology, Salamanca, Spain

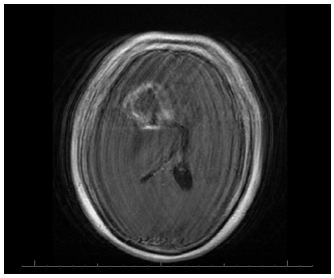
Background and aims: To report an exceptional case of encephalic toxoplasmosis (ET) resembling glioblastoma as initial manifestation of HIV-infection.

Case Report: A 50-year-old man consulted for a 10 days long clinical picture of behavioral disturbances and pharmaco-refractory headache. Past medical history was remarkable by 8 month-course of constitutional syndrome with normal blood test, thoraco-abdomino-pelvic CT-scan, and colonoscopy.

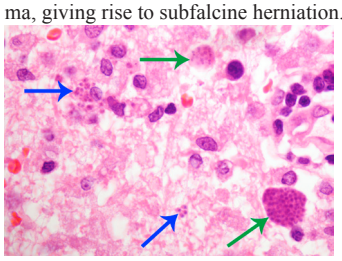
Results: Neurological examination only highlighted drowsiness, but cranial CT-scan (and MRI later), showed a right fronto-parietal infiltrative mass, with annular enhancement, invading contralateral hemisphere through corpus callosum, causing midline shift. After performing stereotactic lesion biopsy, immunohistopathology revealed Toxoplasma intracellular bradyzoites and extracellular tachyzoites, besides HIV-antigen presence using anti-HIV p24-antibody. Laboratory analyses disclosed positive anti-toxoplasma-IgG, 262 CD4/μL, and 747.604 copies/mL viral load. Anti-Toxoplasma and antiretroviral therapies were initiated. Finally the patient achieved complete remission.



Cranial CT-scan (axial slice: after intravenous contrast application). It became apparent an extensive fronto-parietal hypodensity with mass effect, reaching the contralateral hemisphere in a "butterfly-like" mode, and producing midline displacement.



Gadolinium-enhanced T1-weighted MRI (axial slice). The results of the MRI confirmed the findings on CT-scan, defining the lesion as a large intra-axial ring-enhancing mass and extensive surrounding edema, giving rise to subfalcine herniation.



Cerebral tissue sample. In optical microscope, free tachyzoites (blue arrows) and pseudocyst bradyzoites (green arrows) around necrotic lesions were observed (HE stain, x100). These formations tested positive for anti-Toxoplasma immunohistochemical stain.

Conclusion: Glioblastoma is the commonest primary brain neoplasm in adults. Furthermore, ET (AIDS-defining illness) is generally a late HIV-infection complication that usually results from latent infection reactivation. Common ET clinical presentations are cephalalgia and focal neurological deficit. Its onset rarely precedes HIV-infection diagnosis. Only 14-25% of patients show a single lesion, moreover, AIDS patients may have ET in abnormal locations. Definitive diagnosis procedure is brain biopsy which is justified in cases of atypical radiologic appearance for ET. To our knowledge, this is the first described case with these neuroradiological features and >200 CD4/μL heralding AIDS. Consequently, clinicians must consider this possibility before a ring-enhancing space-occupying cerebral lesion, even in patients without prior immunosuppression or HIV-infection history, in order to bring about early diagnosis and treatment administration.

Disclosure: Nothing to disclose

P2235

Central nervous system tuberculosis: a three-decade analysis.

M.J. López-Martínez[1], L. Martínez-García[2], M. Bordallo[2], E. Navas[3], C. Quereda[3], G. Garcia-Ribas[1], E. Gómez-Mampaso[2], Í. Corral[1]

[1]Hospital Universitario Ramón y Cajal, Neurology, Madrid, Spain, [2]Hospital Universitario Ramón y Cajal, Microbiology, Madrid, Spain, [3]Hospital Universitario Ramón y Cajal, Infectious Diseases, Madrid, Spain

Background and aims: Tuberculous meningitis (TBM) is an uncommon but severe complication of tuberculous infection, due to a high rate of morbidity and mortality despite adequate treatment. Immunosuppression is the most important risk factor for the development of neurological tuberculous disease.

Methods: Retrospective review of epidemiology, clinical manifestations, laboratory features, neuroimaging, treatment regimen and clinical outcome of patients with definite central nervous system (CNS) tuberculosis (Mycobacterium identification in cerebrospinal fluid (CSF) or in biopsy material), in a tertiary hospital from 1979 to 2013. We compare human immunodeficiency virus (HIV) infected and HIV-negative groups.

Results: A total of 63 subjects was included: 61 TBM (4 associated with tuberculous brain abscess (TBA), 1 isolated TBA and 1 isolated tuberculoma. Among TBM cases: 61% were male, mean age was 43 years [32-66] and 59% had active extraneurological tuberculosis. Median CSF white blood cell count was 160 cells/μl [66-345], glucose 21 mg/dl [19-41] and protein 1.7 mg/dl [1.1-2.5]. Neuroimaging was normal in 44%. Multidrug resistance was found in 3 HIV-positive patients. Antituberculous treatment was administered a mean of 6 days [2-23] after CSF analysis. Permanent neurological sequelae occurred in 38% and mortality was 23%. HIV-positive patients (21) were younger, had extraneurological tuberculosis and developed TBA more frequently (4 of 5 TBA). They presented more neurologic sequelae, but mortality was similar to the HIV-negative group.

Conclusion: CNS tuberculosis is frequently associated to HIV infection, but this association does not affect mortality, clinical manifestations or ancillary tests results. TBA is a characteristic complication in HIV-positive patients.

Disclosure: Nothing to disclose

P2236
Guillain-Barré syndrome following acute hepatitis E in a Western European man

P. Pérez Torre, F. Acebrón, E. Monreal, E. Viedma Guiard, P. Martinez Ulloa, C. Estévez Fraga, A. Alonso Cánovas, I. Avilés Olmo, J. Buisán Catevilla
Hospital Ramón y Cajal, Neurology, Madrid, Spain

Background and aims: In Europe and North America, hepatitis E is known as an acute disease in travellers returning from tropical countries, but an endemic source of hepatitis E has always been suspected. Here, we report one of the few cases of GBS due to local acute hepatitis E virus (HEV) infection associated with the presence of anti-ganglioside GM1 antibodies in immunocompetent male of Western Europe.

Case Report: A 54-year-old previously healthy man presented with Guillain-Barré syndrome (GBS) and elevated liver enzymes. As epidemiological data he had been bitten a month earlier by a dog and raised a pig in the backyard. The patient presented with tetraparesis. Further diagnostic investigations showed HEV acute infection confirmed serologically and by polymerase chain reaction (PCR) from blood .

Results: The presence of an acute hepatitis E infection was associated with anti-ganglioside GM1 antibodies. After treatment with intravenous immunoglobulins, the patient made a rapid recovery.

Conclusion: The actual incidence of GBS associated with HEV infection is unknown because native hepatitis E is still underdiagnosed in Western Europe. Since the patient reported no travel history, it seems likely that the HEV infection was locally acquired. Despite having been bitten by a dog we consider it most probably resulted from touching an infected pig since HEV infection is endemic in the Spanish swine population, not so in dogs. Therefore we strongly recommend that testing for HEV should be included routinely even in Western Europe, in the diagnostic algorithm of GBS when liver function is altered.

Disclosure: Nothing to disclose

P2237
Abstract cancelled

Movement disorders 6

P2238

Effects of coenzyme Q10 in PSP, A multicenter, randomized, placebo-controlled, double-blind study

D. Apetauerova[1], S. Scala[1], D. Standaert[2], R. Hamill[3], D. Simon[4], T. Yacoubian[5]
[1]Lahey Hospital and Medical Center, Neurology, Burlington, MA, USA, [22]University of Alabama at Birmingham, Neurology, Birmingham, USA, [33]University of Vermont College of Medicine, Neurological Sciences, Burlington, VT, USA, [4]Beth Israel Deaconess Medical Center & Harvard Medical Center, Neurology, Boston, MA, USA, [52]University of Alabama at Birmingham, Neurology, Birmingham, AL, USA

Background and aims: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder clinically classified as an atypical parkinsonian syndrome or neuropathologically as a tauopathy. Mitochondrial dysfunction is hypothesized to play a role in the pathophysiology of PSP. CoQ10, a potent antioxidant found in humans, is the coenzyme for mitochondrial enzymes (complexes I, II & III) as well as other cellular enzymes. An investigator initiated, multicenter, randomized, placebo-controlled, double-blind clinical trial to determine whether Coenzyme Q10 (CoQ10) is safe, well tolerated, and effective in slowing functional decline in PSP.

Methods: 61 participants received CoQ10 (1200mg/day) or placebo for up to 12 months. The Progressive Supranuclear Palsy Rating Scale (PSPRS), Unified Parkinson's Disease Rating Scale (UPDRS), Activities of Daily Life (ADL), Mini Mental Status Exam (MMSE), Parkinsons Disease Quality of Life Scale (PDQ-39), and SF-36 were monitored at baseline and subsequently at months 3, 6, 9 and 12. The safety profile of CoQ10 was determined by adverse events, vital signs, and clinical laboratory values. Primary outcome measures were change in PSPRS and UPDRS scores from baseline at month 12.

Results: CoQ10 was well tolerated. No statistically significant differences were noted between the CoQ10 and placebo groups in the primary or secondary outcome measures. A non-significant trend toward slower clinical decline in the CoQ10 group was observed in total PSPRS among those participants who completed the trial.

Conclusion: High doses of CoQ10 did not show statistically significant improvement of PSP symptoms or disease progression. The trend towards slower clinical decline in the total PSPRS in the CoQ10 groups is of uncertain significance.

Disclosure: This study was supported by grants from the Society for PSP and the Robert E. Wise Research and Education Institute. The CoQ10 and matching placebo were formulated, manufactured and packaged with minimal cost by Vitaline® Formulas (Green Bay, WI) and Kaneka (Pasadena, TX)

P2239

Clinical aspect of botulinum treatment discontinuation in focal dystonia

M. Balaz[1], E. Ehler[2], M. Bares[1]
[1]Brno, Czech Republic, [2]Pardubice Hospital, Pardubice, Czech Republic

Background and aims: Botulinum toxin (BoNT) therapy is considered to be a first-line, best and standard treatment of focal dystonia. Despite this fact, drop-out rates from the treatment appear to be quite high. Aim of our work was to compare reasons for BoNT discontinuation in focal hand dystonia (FHD) and cervical dystonia (CD).

Methods: We included 630 patients, 80 of them with FHD and 550 with CD examined in two movement disorders centers. We inititiated survey on effectivity of treatment and reasons for discontinuation of BoNT therapy where applicable. All patients with BoNT treatment were followed for at least 3 years.

Results: Of patients initiated with BoNT only about 60% continued with treatment for more than 5 treatment cycles. Main diference between the groups was the incidence of side effects, which was the most frequent cause (27%) of BoNT discontinuation in FHD. In CD group, only 13.4% of patients reported side effects (p 0.047). Most relevant reported side effect in both groups was muscle weakness (85%).

Conclusion: Relatively high proportion (53%) of patients with FHD chose to discontinue the treatment with BT. This was not statistically different in comparison to CD (44%). Our results imply that it is important to pay attention to occurrence especially of side effects in patients with FHD. Improvement of treatment procedure by adjusting a BoNT dose or improvement of the application is warranted.

Disclosure: Nothing to disclose

P2240

Significant reduction of pain treatments with safinamide administered as add-on therapy to levodopa in patients with Parkinson's disease and fluctuations.

P. Barone[1], C. Cattaneo[2], R. La Ferla[2], E. Bonizzoni[3], M. Sardina[4]

[1]University of Salerno, Department of Medicine, Neuroscience Section, Baronissi (Salerno), Italy, [2]Zambon SpA, Medical Department, Bresso (Milan), Italy, [3]University of Milan, Department of Clinical Science and Community, Section of Medical Statistics and Biometry "G.A. Maccacaro", Milan, Italy, [4]Zambon SpA, R&D Department, Bresso (Milan), Italy

Background and aims: Safinamide (Xadago™, Zambon SpA, Italy), a unique molecule with a novel mechanism of action (dopaminergic and non-dopaminergic), was studied in late-stage PD patients in two double-blind, placebo-controlled, 6-months trials (016 and SETTLE), showing an increase in "ON" time and a decrease in "OFF" time without increasing troublesome dyskinesia. The objective of this post-hoc analysis is to evaluate the efficacy of safinamide vs. placebo on pain in Parkinsonian patients with motor fluctuations.

Methods: The effects of safinamide on the reduction of concomitant pain treatments and on the bodily discomfort domain of the Parkinson's Disease Quality of life questionnaire PDQ-39 were investigated using the pooled data from the pivotal Phase III trials 016 and SETTLE.

Results: The percentage of patients with no pain treatments at the end of the trials were significantly lower in the safinamide group compared to the placebo group (76.1 vs 70% respectively, p=0.03053). Moreover, safinamide showed significant improvements in the bodily discomfort domain (p=0.0007) of the PDQ-39 scale.

Conclusion: Safinamide, administered as add-on therapy to levodopa in mid- to late-stage fluctuating PD patients, contributed to reduce the number of concomitant pain treatments and to improve the bodily discomfort domain of the PDQ-39 score, with a significant positive impact on the quality of life of the patients.

Disclosure: Carlo Cattaneo, Roberto La Ferla and Marco Sardina are employees of Zambon Pharma SpA. Erminio Bonizzoni is a consultant for statistical analyses of Zambon SpA. Paolo Barone is consultant and member of the Scientific Advisory Board of Zambon SpA.

P2241

Exploring indexes of driving performance in cognitively intact drivers and drivers with Parkinson's disease (PD)

I. Beratis[1], N. Andronas[1], E. Papadimitriou[2], D. Pavlou[2], M. Stamelou[1], G. Tsivgoulis[1], L. Stefanis[1], S. Papageorgiou[1]

[1]Athens Medical School, "Attikon" University Hospital , [2]nd Department of Neurology, Athens, Greece, [2]National Technical University of Athens, School of Civil Engineering, Department of Transportation Planning and Engineering, Athens, Greece

Background and aims: Previous research has provided evidence about the presence of driving difficulties in drivers with Parkinson's disease (PD). In the present research we explored in detail the driving profile of individuals with PD by applying a large driving simulation experiment.

Methods: Inclusion criteria required a valid driver's license, regular car driving, a CDR score ≤0.5, and a Hoehn&Yahr score ≤3. 41 cognitively intact individuals (Age: 59.8±9.1 years) and 19 individuals with PD (Age: 62.7±11.1 years) participated in the study. The data collection included a comprehensive neurological/neuropsychological assessment and a driving simulation experiment. Drivers with PD were tested during the on-phase. Outcome measures were average driving speed, speed variation, wheel position variation, number of crashes, reaction time in unexpected incidents, lateral position, lateral position variation, average headway distance, and headway distance variation.

Results: Significant differences were found in average speed (p=.002), speed variation (p=.048), reaction time (p=.001), average headway distance (p<.001), headway distance variation (p=.004), and wheel position variation (p=.027). The cognitively intact group had greater average speed, speed variation and variation of the wheel position as compared to the group of drivers with PD. On the contrary, the clinical group had increased reaction time as well average headway distance and headway distance variation.

Conclusion: The results of the present study indicate that the driving patterns of individuals with PD differ significantly from those of healthy individuals in indexes that may play an important role in overall driving performance and behaviour.

Disclosure: Nothing to disclose

P2242

Marked intrafamilial variability of ataxia and hypogonadotropic hypogonadism cause by RNF216 mutation

S. Bohlega[1], M. Alqwaifly[2], H. Murad[1], F. Alkuraya[3]
[1]Riyadh, Saudi Arabia, [2]KFSH & RC, Neurosciences, Riyadh, Saudi Arabia, [3]KFSH & RC, Genetics, Riyadh, Saudi Arabia

Background and aims: The syndrome of ataxia and hypogonadism is a rare disorder initially described by Gordon Holmes and recently it was found to be caused by a mutation in RNF2156, STUB1, or PNPLA6. Many other clinical features are associated with these disorders.

Objective: To describe the phenotype and genotype of a new family.

Methods: A positional cloning approach utilizing genome-wide linkage, homozygozity mapping and whole exome sequencing was used.

Results: A native Saudi Arabian family with 2 out of 9 siblings; parents are consanguineous. The first had poor development of secondary sexual characteristics but no ataxia. Cerebellar atrophy and mild white matter lesions were seen on brain MRI. In the second, progressive ataxia was noted at the age of 24 with feature hypogonadism and gynecomastia; moderate cognitive impairment and hyper reflexia were noted. Marked cerebellar atrophy and severe white matter involvement were noted. Serum testosterone level were low but no other pituitary access were affected. Whole body x-ray indicated marked delay in corresponding bone age. Exome sequencing performed from both patients and showed homozygous splice mutation in RNF216,c.2061G>A.

Conclusion: The inheritance pattern in this family was autosomal recessive. There was marked clinical and radiological variabilities among the affected members. The mutation noted was novel and will add to the known mutation reported in this disorder.

Disclosure: Nothing to disclose

P2243

Normal pressure hydrocephalus: increase of oVEMP/utricular input in responders to diagnostic lumbar puncture – evidence for otolith dysfunction?

N. Böttcher, T. Bremova, A.-M. Ruppert, C. Heinze, R. Schniepp, M. Strupp
University of Munich, Neurology, Munich, Germany

Background and aims: Normal pressure hydrocephalus (NPH) is characterized by an impairment of gait and retropulsion. Similar symptoms are also found in patients with impaired otolith function. Therefore, we investigated otolith function using vestibular evoked myogenic potentials (VEMP) (ocular VEMP (oVEMP) for utricular and cervical VEMP (cVEMP) for saccular function) in patients with probable NPH before and after spinal tap test (sTT).

The aim of this study is to investigate whether there is a change in o/cVEMP in responders versus non-responders to sTT in patients with suspected NPH.

Methods: In 25 patients (6 females, age 62-83yrs, mean 76yrs) VEMPs were measured before and after sTT. Patients with an increase of >20% of preferred walking velocity were classified as responders (n=10). As controls, VEMPs were also measured in 11 non-NPH patients before and after sTT.

Results: All patients had reproducible oVEMP; only 16 out of the 25 patients (68%) had cVEMP. There was a significant increase of the peak-to-peak oVEMP amplitude after sTT in responder from 8.5±2.7μV to 18.9±7.5μV (p=0.010). No significant changes were found in non-responder (10.9±6.8μV vs 11.1±7.1μV), in controls (10.7±5.5μV vs 10.2μV±2.9) and for the cVEMP (responder: 41.5±17.5μV vs 49.4±10.4μV; non-responder: 41.0±25.7μV vs 44.1±75.6μV).

Conclusion: 32% of patients with suspected NPH had impaired otolith function. Responders to sTT only had a significant increase of oVEMP and thereby utricular input, probably due to decreased pressure. Both findings indicate that otolith dysfunction may contribute to imbalance in NPH and that an increased utricular function after sTT may be important for gait improvement.

Disclosure: Nothing to disclose

P2244

Abstract cancelled

P2245

Impulse control disorders and side of motor symptoms in Parkinson's disease

M. Calejo[1], A. Rua[2], I. Moreira[3], A. Gonçalves[1], J. Damasio[1], N.M.D.S. Vila-Chã[2], A. Bastos Lima[2], A. Mendes[2], S. Cavaco[1]

[1]Centro Hospitalar do Porto - Hospital de Santo António, Neuropsychology Unit, Porto, Portugal, [2]Centro Hospitalar do Porto - Hospital de Santo António , Neurology, Porto, Portugal, [3]Centro Hospitalar do Porto - Hospital de Santo António, Neuropsychology, Porto, Portugal

Background and aims: Impulse control disorders (ICD) are frequent in Parkinson's disease (PD) and have been linked to changes in the ventral striatum and ventromedial prefrontal cortex. The literature on ICDs association with side of motor symptoms in PD is scarce and inconsistent. We aimed to explore this association with a PD cohort.

Methods: We evaluated 299 consecutive patients diagnosed with PD from the movement disorders' outpatient clinic [51% men; mean age=69±11; mean education=6±4; mean age at onset=60±12; 46% left and 54% right side motor symptoms at onset; mean disease duration=9±6; mean Unified Parkinson's Disease Rating Scale-III (UPDRS-III) off=34±12 and on=23±10; mean levodopa equivalent dose (LED)=884±544mg; 40% were taking dopamine agonists]. Presence of ICD and/or related-behaviors (ICDRB) was screened using the Questionnaire for ICD in Parkinson's Disease-Current-Short (QUIP). Chi-square test and multiple logistic regression analysis were applied for data analysis.

Results: ICDRB were identified in 54 patients (18%). The presence of ICDRB was more frequent in patients with motor symptom onset on the right side than on the left side (23.5% vs 11.7%, p=0.008). This association remained statistically significant (adjusted odds=2.694, p=0.008), when controlled for sex, age at disease onset, UPDRS-III off, LED, and dopamine agonists.

Conclusion: PD patients with motor symptom onset on the right side of the body, which corresponds to greater dopaminergic denervation on the left hemisphere, have an increased risk of developing ICDRB. This finding suggests that excessive pharmacologic stimulation of the preserved right mesocorticolimbic structures triggers the occurrence of ICDRB.

Disclosure: Nothing to disclose

P2246

Brain structural and functional abnormalities in Parkinson's disease patients with freezing of gait

E. Canu[1], F. Agosta[1], E. Sarasso[1], M.A. Volonté[2], L. Sarro[1], S. Galantucci[1], S. Basaia[1], R. Gatti[3], A. Falini[4], G. Comi[2], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Laboratory of Movement Analysis, Milan, Italy, [4]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To assess brain functional and structural network alterations in Parkinson's disease with freezing of gait (PD-FoG).

Methods: T1-weighted, diffusion tensor (DT) MRI and resting state (RS) fMRI were obtained from 23 PD-FoG patients and 36 controls. Subjects underwent clinical, motor-functional, and neuropsychological evaluations. Gray matter (GM) volume and white matter (WM) damage were assessed using voxel-wise approaches. RS fMRI data were analyzed using a model free approach investigating sensorimotor, visual and cognitive brain networks. DT MRI measures were obtained from the main interhemispheric and long-associative WM tracts.

Results: Patients presented mild FoG. Compared with controls, patients showed WM damage mainly of the locomotor pathways, corpus callosum and cingulum. No GM atrophy was detected in patients relative to controls. RS fMRI analysis showed that PD-FoG was associated with a decreased functional connectivity in the sensorimotor, associative-visual, default-mode, and ventral-attentive networks. In patients, reduced functional connectivity was related to the damage of the WM tracts passing through the networks. More severe FoG was associated with lower functional connectivity within the associative-visual network. Worse motor and cognitive performances were related with more severe WM damage and reduced functional connectivity.

Conclusion: PD-FoG patients showed disrupted structural and functional connectivity of the locomotor, associative-visual, and cognitive-related brain networks, which was related to FoG, disease severity, executive and visuospatial deficits. These findings support the theory of FoG as the result of a poor integration between motor programming, visuospatial and attentional abilities.

Disclosure: Jacques and Gloria Gossweiler Foundation.

MS and related disorders 5

P2247

Quality of life and cognitive function in pediatric and young multiple sclerosis patients: a cross-sectional study

A. Carotenuto[1], A. Chiodi[1], V. Magri[1], A. Napolitano[1], T. Costabile[1], C.V. Russo[1], M. Moccia[1], R. Liuzzi[2], K. Piscopo[1], L. Rosa[1], M. Ottobre[1], N. Rainone[3], M.F. Freda[3], P. Valerio[1], V. Brescia Morra[1], R. Lanzillo[4]

[1]Federico II University, Naples, Italy, Department of Neurosciences, Reproductive Science and Odontostomatology, , Naples, Italy, [2]Institute of Biostructure and Bioimaging, National Research Council, Naples, Italy, [3]Federico II University, Naples, Italy, Department of Humanistic Study, Naples, Italy, [4]Naples, Italy

Background: Multiple sclerosis (MS) is a demyelinating disease of the CNS occurring in children or adolescents in approximately 5% of cases. It has been reported cognitive impairment (CI) in 40-54% of early-onset MS patients (EO-MS) and lower health-related quality of life (QOL).

Objective: Assess the relationship between cognitive function and QoL in EO-MS.

Methods: This is a cross-sectional study carried out on 59 EO-MS. Pediatric Quality of life inventory Version 4.0, Beck Depression Inventory II (BDI II) and the Brief Repeatable Battery were performed.

Results: Demographic and clinical characteristics are summarized in table 1. 39% had no CI, 61% had a borderline/significant CI. No association was found between CI and any socio-demographic and clinical data.

HR-QoL was higher in pediatric (age at onset <18y) than young (age at onset 18<x<25) MS patients (p=0.02), and it was inversely related to EDSS (p=0.0005) and Multiple Sclerosis Severity score (MSSS) (p=0.0001). BDI was lower in pediatric than young MS patients and it was directly related to EDSS and MSSS. HR-QoL total score is not related to CI nor to any domain-specific cognitive function even considering BDI as possible bias. CI was related to social , physical functioning score and EDSS (p=0.01) at a logistic regression backward stepwise estimation.

Subjects	59
Female sex, N (%)	31 (52,54)
Age, mean ± SD (years)	20 ± 3,6
Age at onset, mean ± SD (years)	17,24 ± 3,57
Age atonset, subgroup*	
Pediatric (=18y), N (%)	34 (62,96)
Juvenile (18y<x<25y), N (%)	20 (37,04)
Diseaseduration, median (years)	2
EDSS, median (Range)	2,5
MSSS, mean ± SD	5,88 ± 1,44
LesionalLoad*	
Low, N (%)	4 (12,90)
Medium, N (%)	17 (54,84)
High, N (%)	10 (32,26)

Table 1.

Conclusion: We confirmed results of previous papers, pointing out, in addition, that cognition in EO-MS is influenced by physical disability and poor social involvement (school, education, work…). Social participation, affective relations and psychological flexibility could have a protective function on CI.

Disclosure: Nothing to disclose

P2248

Differential recovery from relapse between treatment groups in the CONFIRM study of delayed-release dimethyl fumarate

A. Chan[1], J.T. Phillips[2], R.J. Fox[3], A. Zhang[4], J. Potts[4], N.C. Kurukulasuriya[4]

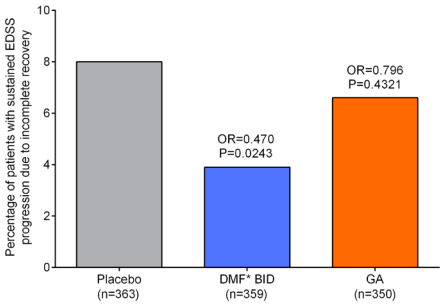
[1]St. Josef Hospital, Ruhr University, Bochum, Germany, [2]Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, USA, [3]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, USA, [4]Biogen Idec, Cambridge, USA

Background and aims: Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated significant efficacy and an acceptable safety profile in relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE and CONFIRM studies. The objective of this analysis was to evaluate the association between relapse and disability progression, and between progression/relapse status and quality of life (QoL) outcomes, in a post-hoc analysis of data from CONFIRM.

Methods: Eligibility criteria included age 18−55 years, RRMS diagnosis, and Expanded Disability Status Scale (EDSS) score 0−5.0. Patients were randomized to receive placebo, DMF 240mg BID or TID, or glatiramer acetate (GA; reference comparator). Odds of relapse-led disability progression (12-week confirmed disability progression beginning within 180 days after the start date of relapse) were assessed using logistic regression adjusted for baseline covariates. Changes from baseline in the Physical and Mental Component Summaries (PCS/MCS) of the Short Form-36 and visual analog scale (VAS) were assessed. Results from patients receiving DMF BID (approved maintenance dose in all regions) are reported.

Results: The intent-to-treat population comprised 363, 359, and 350 patients in the placebo, DMF BID, and GA groups, respectively. At 2 years, the proportion of patients with relapse-led disability progression was lowest in the DMF BID group (Figure 1). PCS, MCS, and VAS scores were significantly improved in patients with no progression and no relapse compared with patients with relapse and/or progression (Figure 2).

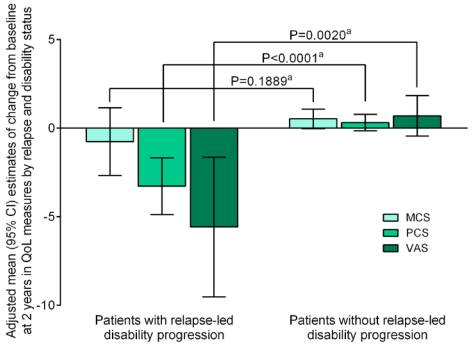
Figure 1. Patients with 3-month EDSS sustained progression within 6 months following an independent neurology committee (INEC)-confirmed relapse at 2 years



*DMF, delayed-release DMF (also known as gastro-resistant DMF)

OR, odds ratio versus placebo, adjusted for baseline EDSS, age (≥40 vs <40 years), number of relapses in the year prior to study entry, and geographic region.

Figure 2. QoL measures by relapse-led disability status.



[a]From ANCOVA model adjusting for corresponding baseline score, age (≥40 vs <40 years), region, and treatment group.

Conclusion: Results suggest that patients receiving DMF had reduced odds of relapse-led disability progression compared with placebo, and that relapse and disability status impact QoL measures.

Disclosure: Study supported by Biogen Idec, Inc.

P2249

Efficacy of teriflunomide treatment in achieving no evidence of disease activity over a 2-year period: post hoc analysis of the TEMSO study

A. Chan[1], J. de Seze[2], P. Truffinet[3], K. Thangavelu[4], P. Rufi[3], M. Comabella[5]

[1]St. Josef Hospital, Klinikum der RUB, Bochum, Germany, [2]Strasbourg University, Hôpital Civil, Strasbourg, France, [3]Genzyme, a Sanofi company, Chilly-Mazarin, France, [4]Genzyme, a Sanofi company, Cambridge, USA, [5]Vall d'Hebron University Hospital, Barcelona, Spain

Background and aims: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS. This post hoc analysis evaluated the efficacy of teriflunomide in achieving no evidence of disease activity (NEDA) in TEMSO (NCT00134563), a pivotal phase 3 study vs placebo.

Methods: Patients with relapsing forms of MS (N=1088) were randomized to teriflunomide 14mg (n=359), 7mg (n=366), or placebo (n=363) for 108 weeks. For each year and over the full 2-year study period, the proportion of patients with a composite measure of NEDA (defined as no gadolinium-enhancing T1 lesions, no new/enlarging T2 lesions, no clinical relapse, and no 12-week sustained disability progression) was reported using odds ratio (OR) and P value for teriflunomide 14mg and 7mg vs placebo.

Results: In year 1, NEDA was observed in 34.4% of patients receiving teriflunomide 14mg vs 22.0% receiving placebo (OR 1.85; P=0.0002) and in 28.8% receiving teriflunomide 7 mg (OR 1.43; P=0.0371). In year 2, NEDA was observed in 35.3% of patients receiving teriflunomide 14mg vs 21.2% receiving placebo (OR 2.03; P=0.0002) and in 29.9% receiving teriflunomide 7mg (OR 1.59; P=0.0162). Over the complete 2-year study period, the proportion of patients with NEDA was significantly higher in the 14mg group (22.9%; OR 1.78; P=0.0031) vs placebo (14.3%). The proportion with NEDA was also higher with teriflunomide 7mg (18.4%; OR 1.34) but not statistically significant.

Conclusion: Teriflunomide was associated with a significant dose-dependent increase in the proportion of patients with NEDA in the first year that persisted in the second year.

Disclosure: Study supported by Genzyme, a Sanofi company.

P2250

Devenir: observational study of detection and assessment of demyelinating events in France

R. Colamarino[1], J.-M. Visy[2], J.-J. Pere[3], I. Bourdeix[4], G.L. Defer[5]

[1]Centre hospitalier Vichy, Neurology, Vichy, France, [2]office based neurologist, Rheims, France, [3]Novartis Pharma, Clinical research, Rueil-malmaison, France, [4]Novartis Pharma, Biometry, Rueil-Malmaison, France, [5]CHU Côte de Nacre, Neurology, Caen, France

Background and aims: Detection and assessment of a first clinical demyelinating event (CSI) in routine practice are currently not well known

This prospective study assessed over 12 months proportion of treated patients with an immunomodulatory (IMD) among those with a first clinical demyelinating event.

Methods: Observational study in France conducted by a representative sample of neurologists on patients for whom first clinical demyelinating event has been diagnosed and who will be followed over 12 months. Nature and frequency of diagnostic tools, decision factors of IMD treatment and use of optional tools evaluating fatigue (U-FIS), behavioral disorders (HAD) and cognitive disorders have been recorded.

Results: Diagnosis tools were used with the following frequency: MRI (100%), lumbar punction (69.3%), evoked potential (48.9%). Out of 137 patients analyzed, 66 (48.2%) have initiated IMD. The most frequent decision criteria for IMD treatment were MRI (77.3%), clinical symptoms (59.1%) and the estimated risk of relapse (45.5%). Fatigue (U-FIS)) and behavioral disorders (HAD) were evaluated for 59% of patients, but cognitive disorders were rarely assessed.

Conclusion: Initiation of IMD treatment in multiple sclerosis for half of the patients within the year following the first clinical demyelinating event is mainly based on MRI criteria and/or the occurrence of a relapse. At MRI the first spatiotemporal dissemination criteria was satisfied for almost 75% of treated patients, but 40% of patients have not been treated despite the presence of this criteria.

Disclosure: This study was granted by Novartis Pharma S.A.S.

P2251

Endothelin-1 serum levels are increased in patients with multiple sclerosis

C. Criscuolo[1], R. Lanzillo[1], A. Cianflone[1], E. Postiglione[1], R. Liuzzi[2], G. Vacca[1], O. Caporale[3], R. Palladino[3], M. Triassi[3], M. Vastola[1], M. Moccia[4], G. Puorro[1], A. Marsili[1], M. Incoronato[5], M. Salvatore[6], V. Brescia Morra[1]

[1]Federico II University, Neurosciences, Reproductive and Odontostomatological Sciences , Naples, Italy, [2]Institute of Biostructure and Bioimaging, National Research Council, Naples, Italy, [3]Federico II University, Department of Public Health, Naples, Italy, [4]Naples, Italy, [5]IRCSS SDN Foundation, Naples, Italy, [6]Federico II University, Advanced Biomedical Sciences, Naples, Italy

Background: Clinical and experimental evidence suggests that endothelin-1 (ET-1) plays a role in cardiac and vascular disease. Patients with multiple sclerosis (MS) show global cerebral hypoperfusion.

Objectives: To evaluate ET-1 in MS patients vs healthy subjects (HS) in the context of a larger study on the association among MS, amyotrophic lateral sclerosis (ALS), and vascular changes at molecular, genetic, anatomic and functional level, over 3 years.

Methods: After two years, we recruited 300 MS patients, 46 ALS patients and 178 HS. Serum ET-1 levels were coded and assayed with a commercially available ELISA kit in blinded fashion by a laboratory assistant (detection range 0.39–25 pg/mL; R&D Systems).

Results: ET-1 levels were performed in 120 MS patients (79 females, 41 males) and in 125 HS (68 females, 57 males). ET-1 median were significantly higher in MS compared to HS (1.59 vs 1.50 pg/mL, p=0.03) at Mann-Whitney test. When stratified for gender, median ET-1 levels were significantly higher in females MS vs HS (1.58 vs 1.44 pg/mL, p=0.03). ET-1 levels positively correlated with age in female MS vs HS ($p<0.05$) but not in males. ET-1 median were significantly higher in 23 SP vs 97 RR MS subtype (2.10 vs 1.57 pg/mL, p=0.003).

Conclusion: We confirm that serum ET-1 levels are significantly increased in MS patients, especially in women. This finding could help explaining the higher incidence of MS in females and the sex-associated differences in susceptibility to cardiovascular diseases. Correlation of ET-1 levels with SP subtype of disease opens new insights in MS pathogenesis.

Disclosure: Nothing to disclose

P2252

Assessing pathological cutoffs of brain atrophy rates in patients with multiple sclerosis

N. De Stefano[1], M.L. Stromillo[1], A. Giorgio[1], M.L. Bartolozzi[2], M. Battaglini[1], M. Baldini[2], E. Portaccio[3], M.P. Amato[3], M.P. Sormani[4]

[1]University of Siena, Sienna, Italy, [2]Hospital of Empoli, Empoli, Italy, [3]University of Florence, Florence, Italy, [4]University of Genoa, Genoa, Italy

Background and aims: Brain volume (BV) is a valid biomarker of clinical state and progression in neurology. We tried to assess the feasibility of establishing specific cutoff values able to discriminate "physiological" or "pathological" rates of BV loss in multiple sclerosis (MS).

Methods: We analyzed longitudinal MRI datasets of MS patients (n=206, 87% relapsing-remitting, 7% secondary progressive, 6% primary progressive) and healthy controls (HC) (n=35). Brain atrophy rates were computed over a mean follow-up of 7.5 years for MS patients and 6.3 years for HC with the SIENA software and expressed as annualized percent BV change (PBVC/y). A weighted ROC analysis and the Area Under the Curve were used for statistics.

Results: The weighted PBVC/y was -0.51±0.27% in MS patients and -0.27±0.15% in HC ($p<0.0001$). There was a significant age-related difference in PBVC/y between HC older and younger than 35 years of age (p=0.02), but not in MS patients (p=0.8). The cutoff of PBVC/y that could maximize the accuracy in discriminating MS patients from HC was -0.37%, with 67% sensitivity and 80% specificity. According with the observed distribution, values of PBVC/y as measured by SIENA that could define a pathological range were above -0.52% with 95% specificity, above -0.46% with 90% specificity and above -0.40% with 80% specificity.

Conclusion: Our evidence-based criteria provide values able to discriminate presence or absence of "pathological" BV loss in MS with high specificity. Such results could be of great value in clinical setting, particularly in assessing treatment efficacy in MS.

Disclosure: Nothing to disclose

P2253

Verbal fluencies are improved with fampridine treatment in multiple sclerosis

P. Decavel[1], E. Magnin[2], Y. Sagawa[3], L. Chamard[1], E. Berger[4], T. Moulin[1]

[1]Besançon, France, [2]CHRU J. Minjoz , Neurology, Besancon, France, [3]CHU Jean Minjoz, Movement analysis, Besançon, France, [4]CHRU Jean Minjoz, Besançon, France

Background: A recent study suggests an effect of fampridine on cognition, especially on information-processing speed. The aims of this study were to evaluate the effects of fampridine on verbal fluencies in MS patients and to compare the supposed cognitive effect with gait effect.

Methods: 31 MS patients were included with 42% of the patients with the primary progressive form, 45% with the secondary progressive form, and 13% with the relapsing remitting form. The mean EDSS was 5.43. Verbal phonological and semantic fluencies were repeated two times (in one week) before fampridine treatment and two times after fampridine treatment. Gait velocity was measured before and after fampridine treatment. Post-hoc analyses were performed in order to limit impact of the test-retest effect.

Table 1: Summary of the MS group characteristics.

Parameters	MS (n = 31) Mean (SD)
Age (years)	50.0 (11.77)
Sex (M/F)	11 / 20
Weight (kg)	76.97 (16.84)
Height (m)	1.67 (0.09)
BMI (kg.m^{-2})	27.54 (5.19)
Disease duration (years)	8.0 (1.4)
Subtypes of MS	
Primary progressive MS	42%
Secondary-progressive MS	45%
Relapsing-remitting MS	13%
EDSS	5.43 (1.08)

Abbreviations: MS: multiple sclerosis; SD: Standard deviation; BMI: Body Mass Index; EDSS: Expanded Disability Status Scale.

Results: Verbal fluencies were significantly improved by fampridine treatment ($p<0.05$). Phonological fluency showed greater improvement than semantic fluency after fampridine treatment. No significant difference on verbal fluency performance was observed between gait respondent and non-respondent groups.

Table 2: Verbal fluencies and gait performances. In white the mean scores and standard deviation before and after fampridine treatment. In gray, *p* values of the comparisons between conditions;in bold significant differences (i.e. p<0.05).

	Pre 1 7 days before fampridine	Pre 2 fampridine treatment begins	Post 1 14 days after fampridine	Post 2 21 days after fampridine	Pre 1 vs Pre 2	Pre 1 vs Post 1	Pre 1 vs Post 2	Pre 2 vs Post 1	Pre 2 vs Post 2	Post 1 vs Post 2
Semantic fluency										
Animals 1 min (w)	16.26 (5.54)	16.45 (5.03)	17.94 (4.96)	17.97 (5.42)	0.994	0.127	0.116	0.211	0.195	1.000
Animals 1-2 min (w)	8.81 (4.98)	9.19 (5.21)	8.52 (4.92)	10.00 (4.06)	0.954	0.980	0.379	0.798	0.698	0.196
Animals total (w)	25.06 (9.00)	25.65 (9.25)	26.45 (8.97)	27.97 (8.31)	0.950	0.575	**0.042**	0.878	0.145	0.500
Phonological fluency										
P 1 min (w)	12.45 (3.76)	14.06 (5.16)	14.84 (4.69)	14.71 (4.74)	0.115	**0.007**	**0.011**	0.700	0.803	0.998
P 1-2 min (w)	6.97 (3.23)	6.45 (3.03)	7.87 (4.78)	8.52 (3.69)	0.818	0.424	**0.049**	0.083	**0.004**	0.695
P total (w)	19.39 (6.04)	20.52 (7.52)	22.71 (8.7)	23.23 (7.74)	0.656	**0.006**	**0.001**	0.119	**0.034**	0.952
Gait analysis										
Gait velocity (m.s^{-1})	0.90 (0.45)	0.94 (0.49)	1.04 (0.51)	NA	0.574	**0.000**	NA	**0.000**	NA	NA

Conclusion: Our results suggest that fampridine has an independent procognitive effect in MS, especially on executive functions and not only on information-processing speed.

Disclosure: Nothing to disclose

P2254

Five-year follow-up data from the French national Copaxone observatory

M. Clanet[1], A. Moulignier[2], C. Pierrot-Deseilligny[3], C. Lebrun-Frenay[4], T. Moreau[5], A. Leizorovicz[6], F. Boutitie[7], P.-H. Depoortere[8], F. Gueyffier[9]

[1]CHU Purpan, Toulouse, France, [2]Fondation Ophtalmologique A. de Rothschild, Paris, France, [3]Hôpital de la Salpêtrière, Paris, France, [4]Hôpital Pasteur, Nice, France, [5]CHU, Dijon, France, [6]Université Claude Bernard, Lyon I, France, [7]Université Claude Bernard, Lyon-Sud, France, [8]Teva Laboratoires, La Défense, France, [9]Faculté de Médecine Laennec, Lyons, France

Background and aims: Information on outcome on patients with multiple sclerosis (MS) treated with immunomodulatory treatments in everyday practice is poorly documented. The objective of this naturalistic cohort study was to describe clinical outcome over time in MS patients starting treatment with glatiramer acetate (GA) in France.

Methods: A representative sample of hospital- and community- based neurologists in France was invited to participate in the study. All adult patients with a diagnosis of relapsing-remitting MS and starting treatment with GA for the first time were eligible. Patients were followed up according to the physician's everyday practice. Data were documented at yearly study visits and included relapses, EDSS score, treatments, hospitalisations, consultations, sick leave and adverse events.

Results: 852 patients were enrolled between 2005 and 2008. 594 (69.7%) were followed for at least 4.5 years, of whom 260 were still receiving GA. The median GA treatment duration was 3.4 years. The principal reasons for treatment discontinuation were inadequate efficacy (38.9% of discontinuations) and poor tolerability (35.6%). 37.2% of patients did not experience a relapse during follow-up. The annualised relapse rate decreased from 0.64 relapses/year at year 1 to 0.28 at year 5. Progression of disability occurred in 31.9% of patients, and 7.9% evolved to secondary progressive MS. No unanticipated safety issue arose.

Conclusion: Treatment persistence in this real-life cohort was somewhat higher than anticipated from other observational studies. Clinical outcome was comparable to that seen in the long-term follow-up of the Phase III clinical study.

Disclosure: The research has been granted by Teva Laboratoires

P2255

The influence of age on the disease phenotype preceding the onset of progressive multiple sclerosis

A. Scalfari[1], C. Lederer[2], M. Daumer[3], R. Nicholas[4], G. Ebers[5], P. Muraro[6]

[1]London, United Kingdom, [2]Sylvia Lawry Centre, Munich, Germany, [3]Silvia Lawry Centre, Munich, Germany, [4]Imperial College, London, United Kingdom, [5]Oxford University , Oxford, United Kingdom, [6]Imperial College , London, United Kingdom

Background and aims: Although primary (PP) and secondary progressive (SP) multiple sclerosis (MS) patients start to progress at similar age, the clinical phenotype before progression is widely variable. We investigated the relationship between age and relapses before the progressive phase.

Methods: By using the London Ontario database we assessed, among 751 progressive MS patients (PP=217; SP=534): 1) the relationship of age with the relapses frequency; 2) the impact of relapses on the age at onset of progression; 3) the influence of age on the evolution of the progressive phase.

Results: Among SP patients, age at onset did not influence the early (first two years) attack frequency (r=-0.05; p=0.13). In contrast, being younger at onset was associated with a longer latency to progression and with a significantly larger number of total attacks before progression (≥4 relapses=27.4 years; 2-3 relapses=31.0 years; 1 relapse=32.8 years; p<0.001). Progressive MS subtypes with no attacks (PPMS) or 1, 2-3 and ≥4 relapses during the relapsing remitting (RR) phase began to progress at similar age (38.6, 41.3, 41.4, 39.2 mean years, respectively). However, the age at start of progressive disease did not affect its evolution.

Conclusion: The age at onset of RRMS strongly influences the pre-progressive course, yet the age at onset of progression is unaffected by the relapses frequency. We suggest redefining progressive MS as a unified disorder, with initially different phenotypes that converge into a progressive course under the dominant influence of age-related mechanisms.

Disclosure: This research was supported by the UK MS Society

Neuroimaging 2

P2256

Functional connectivity alterations and executive and social skills in Neurofibromatosis Type 1

M. Loitfelder[1], I. Veer[2], S. Rombouts[2], H. Swaab[2], M. Van Buchem[3], B. Verbist[3], E. Arkink[3], E. Arkink[3], R. Schmidt[1], S. Huijbregts[2]

[1]*Department of Neurology, Graz, Austria,* [2]*Leiden University, Leiden, The Netherlands,* [3]*Department of Radiology, Leiden, The Netherlands*

Background and aims: Neurofibromatosis Type 1 (NF1) has regularly been associated with cognitive, social and behavioral problems. The fact that many different cognitive and behavioral impairments have been observed in NF1 suggests that networks of brain regions are involved rather than specific brain regions. Here, we examined whether functional connectivity (FC) was different in NF1 and, if so, whether associations were present with cognitive, social and behavioral outcomes.

Methods: 14 NF1 patients (8 male, age: M=12.49, SD=2.65) and 30 healthy controls (HC; 23 male, age: M=12.30, SD=2.94; p=.835) were included. FC was assessed using functional resting state scanning. We analyzed brain regions that have been associated specifically with cognitive and social functions. For NF1-patients, connection strengths between brain regions showing HC-NF1 differences were correlated with parent-reports of cognitive, social and behavioral functioning.

Results: Compared to HC, patients showed differences in FC between the left vACC and the frontal cortex, insula, and subcortical areas (caudate, putamen), between the left amygdala and the frontal cortex, insula, supramarginal gyrus and PCC/precuneus, and between the left OFC and frontal and subcortical areas (caudate, pallidum). In patients, indications were found for associations between increased fronto-frontal and temporo-frontal FC with cognitive, social and behavioral deficits (r-range=0.536-0.851).

Conclusion: NF1 patients showed differences in FC between areas associated with cognitive and social functioning when compared to controls. This, plus the fact that connectivity strengths in these networks were associated with worse cognitive, social, and behavioral outcomes suggests a neuro-pathological basis for the widespread deficits observed in NF1.

Disclosure: Nothing to disclose

P2257

Cognitive and social correlates of cerebral volumetric abnormalities in Neurofibromatosis Type 1

M. Loitfelder[1], I. Veer[2], S. Rombouts[2], H. Swaab[2], R. Schmidt[1], M. Van Buchem[3], S. Huijbregts[2]

[1]*Department of Neurology, Graz, Austria,* [2]*Leiden University, Leiden, The Netherlands,* [3]*Department of Radiology, Leiden, The Netherlands*

Background and aims: Neurofibromatosis Type 1 (NF1) is characterized by social and cognitive problems. MRI-studies have shown focal T2-hyperintensities in white matter and deep grey matter and larger white and grey matter volumes in NF1. This study aimed to elucidate associations between abnormalities observed with MRI and cognitive and social outcomes.

Methods: 15 NF1-patients (mean age 12.9 years, SD 2.6) and 18 healthy controls (HC, mean age 13.8 years, SD 3.6) underwent 3T MRI-scanning. Segmentation of grey and white matter, as well as a range of subcortical nuclei, was carried out. Voxel-based morphometry was performed to assess differences in grey matter density. Correlations were calculated between MRI-parameters and cognitive and social outcomes.

Results: After correction for age, sex, and intracranial volume, larger volumes of all segmented subcortical regions were found in NF1-patients compared to controls. Patients further showed decreased grey matter density in midline regions of the frontal and parietal lobes, and larger total white matter volume. NF1-patients showed more social problems and autistic mannerisms, and poorer executive functioning than HC. In NF1-patients larger left putamen volume and larger total WM-volume were associated with more social problems and poorer executive functioning, larger right amygdala volume with poorer executive functioning and autistic mannerisms, and smaller precentral gyrus GM-density was associated with more social problems. Presence of T2-hyperintensities was not associated with cognitive or social outcomes.

Conclusion: Extensive differences between patients and controls were found in white matter, cortical, and subcortical brain regions, which could be associated with social and executive problems in NF1.

Disclosure: Nothing to disclose

P2258

Microstructural white matter alteration in Neurofibromatosis Type 1 and its association with executive functioning

M. Loitfelder[1], S. Huijbregts[2], I. Veer[2], M. Van Buchem[3], R. Schmidt[1], H. Swaab[2], S. Rombouts[2]

[1]*Department of Neurology, Graz, Austria,* [2]*Leiden University, Leiden, The Netherlands,* [3]*Department of Radiology, Leiden, The Netherlands*

Background and aims: Neurofibromatosis Type 1 (NF1) is characterized by brain volumetric increases and cognitive deficits (particularly executive dysfunction). Moreover, widespread microstructural white matter changes (WM) have been reported, but their relation to executive function has not been investigated so far. We here seek to examine the relation between micro-structural alterations and executive functions in patients and highlight WM group differences.

Methods: We performed diffusion tensor imaging analyses using tract-based spatial statistics in 16 NF1 patients and 32 controls and used a whole brain as well as a region of interest based approach (using bilateral anterior thalamic radiation, ATR), to determine micro-structural group differences. Sub-scores of the Memory-Search-2-Dimensions (MS2D, one of the Amsterdam Neuropsychological Tasks) were correlated with diffusion-parameters.

Results: Bilateral fractional anisotropy (FA), an index of general WM integrity, and the right-hemispheric axial diffusivity (DA), a measure of axonal integrity, of the ATR correlated with MS2D correct responses (FA: right: r=.695, p=0.008; left: r=.615, p=0.025, DA: right: r=.513, p=0.037). In line with previous literature, we identified decreases in FA, and increases in mean diffusivity, radial diffusivity and axial diffusivity in NF1 patients disseminated over the whole brain. Group differences were found significant within ATR for all four measures (p-range: <0.001-0.004).

Conclusion: We here report for the first time on the association between aberrant WM-microstructure within the ATR and executive function in NF1. However, its association with increased WM needs to be further determined.

Disclosure: Nothing to disclose

P2259

Brain atrophy evaluation in multiple sclerosis: change over time of corpus callosum area is more sensitive and reproducible than whole brain volume.

L. Bandieri[1], L. Vuolo[1], A. M. Repice[2], M. Grammatico[1], C. Mechi[2], L. Massacesi[2]

[1]*University of Florence, Neurosciences Drugs and Child Health, Florence, Italy,* [2]*Careggi University Hospital-University of Florence, Neurology 2, Florence, Italy*

Background and aims: Measurement by MRI of whole brain volume (BV) changes over time is commonly used as an in vivo marker of brain atrophy, but its sensitivity and reproducibility is limited, even within individuals. Corpus Callosum (CC) measurement may represent an alternative, but its efficacy has never been compared to BV. In this study longitudinal changes of BV and of CC area and their correlation to disability were compared in multiple sclerosis (MS) patients.

Methods: Relapsing Remitting MS patients (n= 40) were included. Brain MRI were carried out at baseline (T0) and after 5 years (T5). CC area was measured with a semiautomatic method (MIPAV) in the central slice of T2w sagittal MRI scans; in the same patients BV was evaluated with an automated method (SIENA/SIENAX) in T1w scans.

Results: T0 CC area= 549.52mm^2, T5 CC area=505.83mm^2; CC area reduction between T0-T5=7.8%+6.8% (43.7mm^2 +37.6;); CC area correlation between T0 and T5, r=0.96. T0 BV=1,587cm^3, T5 BV= 1,552cm^3; BV reduction between T0-T5=2.2%+4.0 (35.0cm^3+68.3); BV correlation between T0 and T5, r=0.80. CC area but not BV changes resulted correlated to disability progression (OR=0.9; p<0.04).

Conclusion: CC area is a marker of brain atrophy more sensitive, reproducible and closely associated to disability changes than BV. CC area used as an outcome measure can improve both power of clinical trials and individual patient follow up of clinical practice.

Disclosure: Nothing to disclose

P2260

Differential diagnosis of neurodegenerative parkinsonism using magnetic resonance imaging at 1.5 and 3.0 Tesla

C. Müller[1], J. Tashiro[1], A. Hussl[1], M. Schocke[2], C. Scherfler[1], E. Gizewski[3], W. Poewe[1], K. Seppi[1]

[1]*Medical University of Innsbruck, Neurology, Innsbruck, Austria,* [2]*Medical University of Innsbruck, Radiology, Innsbruck, Austria,* [3]*Medical University of Innsbruck, Neuroradiology, Innsbruck, Austria*

Background and aims: While magnetic resonance imaging (MRI) at 3.0 Tesla (T) is increasingly used in the diagnostic work-up of parkinsonian disorders, no studies have assessed its diagnostic potential for differential diagnosis of neurodegenerative parkinsonism in comparison to 1.5T MRI. Our aim is to assess the diagnostic value of 3.0T MRI for the differential diagnosis of Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

Methods: Patients with PD (HY stages <3), MSA, PSP and healthy controls (HC) underwent brain MRI at 1.5 and 3.0T. Blinded to diagnosis and MR field strength, semiquantitative and -qualitative rating of different brain regions was performed. Abnormalities rated as indicative for MSA included putaminal atrophy, T2 putaminal hypointensity, T2 hyperintense putaminal rim, hot-cross-bun sign, MCP atrophy, T2 MCP hyperintensity and cerebellar atrophy, while midbrain atrophy, hummingbird sign and SCP atrophy were rated as signs for PSP.

	PD (H&Y 1-2)	MSA	PSP	HC
Number	21	21	20	21
Sex (m/f)	14/7	12/9	14/6	10/11
Age (years)	62.6 ± 10.2	62.8 ± 8.9	68.1 ± 6.1	66.2 ± 5.9
Disease duration (Years)	4.3 ± 10.2	2.3 ± 1.5	1.9 ± 1.6	NA
Hoehn and Yahr	1.9 ± 0.1	3.2 ± 0.9	3.1 ± 0.8	NA
UPDRS total	30.3 ± 8.2	67.8 ± 12.9	54.6 ± 16.5	NA

Demographical characteristics of study participants (mean ± standard deviation).

Results: Scans positive for MSA at 1.5T revealed good discriminatory power between groups. Sensitivity at 3.0T was 90.5% in distinguishing MSA from PD, PSP and HC, whereas specificity was poor, but improved by excluding putaminal signal changes. MRI scans indicative for PSP showed similar diagnostic accuracies at 1.5 and 3.0T in distinguishing PSP from MSA, PD and HC.

Field strength	Evaluation	MSA	PD	PSP	HC
		n (sensitivity)	n (specificity)		
1.5T	Atrophy patterns° and signal changes*	19 (90.5%)	1 (95.2%)	4 (80%)	0 (100%)
3.0T	Atrophy patterns° and signal changes*	19 (90.5%)	4 (81.0%)	12 (40%)	8 (61.9%)
3.0T	Atrophy patterns°	15 (71.4%)	2 (90.5%)	3 (85%)	0 (100%)

* Signal changes: T2 putaminal hypointensity, T2 hyperintense putaminal rim, hot cross bun sign, T2 MCP hyperintensity.
° Atrophy patterns: putaminal atrophy, MCP atrophy, cerebellar atrophy.

Sensitivity and specificity of scans indicative for MSA in patients with neurodegenerative parkinsonism and HC.

Field strength	Evaluation	PSP	PD	MSA	HC
		n (sensitivity)	n (specificity)		
1.5T	Atrophy patterns°	19 (95%)	1 (95.2%)	4 (81%)	0 (100%)
3.0T	Atrophy patterns°	16 (80%)	0 (100%)	4 (81%)	1 (95.2%)

° Atrophy patterns: midbrain atrophy, hummingbird sign, SCP atrophy.

Sensitivity and specificity of scans indicative for PSP in patients with neurodegenerative parkinsonism and HC.

Conclusion: Rater-based assessment of structural abnormalities in MRI at 3.0T does not seem to yield greater diagnostic accuracy as compared to 1.5T. Evaluation of putaminal signal abnormalities on 3.0T carries a high rate of false positive rates for MSA.

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P2261

Translational imaging in diagnostic workup of neurodegenerative parkinsonian syndrome

C. Paschetta[1], A. Skanjeti[1], F. Buttari[1], M. Iudicello[2], D. Gned[3], V. Podio[1]

[1]S. Luigi Hospital, Nuclear Medicine, Orbassano, Italy, [2]S. Luigi Hospital, Neurology, Orbassano, Italy, [3]S. Luigi Hospital, Radiology, Orbassano, Italy

Background and aims: Movement disorders are common, and neuroimaging plays a pivotal role in diagnosis. Aim of this study was the evaluation of diagnostic accuracy in neurodegenerative parkinsonian syndrome (NPS) of an up-to-date analysis of FP-CIT SPECT and MRI images.

Methods: 62 patients with Parkinson's disease suspicion (age 66±11, 33 M) underwent FP-CIT SPECT and brain MRI within 2 years. Later, neurologist established diagnosis on a clinical base and NPS was confirmed in 31 patients. From the two imaging modalities, images were normalized (with our FP-CIT template and built-in T1 template, respectively) and analyzed by SPM; volume-of-interest data for each modality were extracted with MarsBaR software. Multivariate logistic regression was used to evaluate the correlation of both SPECT and MRI semi-quantitative data with diagnosis.

Results: At SPECT, basal ganglia uptake was significantly lower in NPS compared to NPS-free (p=0.00001). In T1 images, SPM detected difference between the two groups in thalami and in anterior cingulate (p=0.005 and p=0.04, respectively): in both occurrences MR accuracy was lower than SPECT accuracy. Multivariate analysis showed that MRI data of thalami were independently and significantly correlated with diagnosis and improve accuracy from 77% of SPECT alone to 87% (SPECT + MRI). Cingulate data showed to be non significant (probably variable dependent from thalami).

Conclusion: SPECT is mandatory when NPS is suspected; an integrated voxel-based analysis of MR and SPECT by SPM showed to increase accuracy. Translational imaging should be encouraged in order to fully develop the strength of both structural and functional imaging in patients with suspected NPS.

Disclosure: Nothing to disclose

P2262

"Corpus callosum fibers rupture sign" as a neuroimaging biomarker of dementia in Parkinson's disease

K. Mazurenka[1], V. Ponomarev[2], R. Sakovich[3]

[1]Belarusian Medical Academy of Postgraduate Education, Department of Neurology and Neurosurgery, Minsk, Belarus, [2]Belarusian Medical Academy of Postgraduate Education, Head of Department of Neurology and Neurosurgery of Bel-MAPGE, Minsk, Belarus, [3]Minsk City Clinical Hospital № Radiology Department, Minsk, Belarus

Background and aims: Dementia is a common complication of Parkinson's disease (PD), but the specific neuroimaging criteria of dementia in PD (PDD) remain undefined.

Methods: 40 patients with PD (9 demented, 31 non-demented) and 30 healthy controls underwent DTI at 1.5T MRI scanner. Diffusion tensor tractography (DTT) of the corpus callosum (CC) was performed using multiple regions of interest (ROIs). ROIs were drawn at the caudal, middle and ventral substantia nigra (SN), anterior and posterior quadrants of both hemispheres, fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were extracted. Neuropsychological evaluation included MMSE, Frontal Assessment Battery (FAB), Parkinson's Disease-Cognitive Rating Scale (PD-CRS).

Results: PD patients scored lower on the MMSE (27.5+2.2 vs. 28.3+1.5), FAB (15.3+2.5 vs. 16.9+1.3) and PD-CRS (85.5+17.2 vs. 96.8+10.9) than controls. PD patients have shown an increased ADC at the ventral SN (p=0.008) compared to control patients. PDD patients had significantly higher total ADC of all quadrants of the brain (p=0.02), especially posterior quadrants (p=0.001) and the CC (p=0.0006). Using DTT of CC we found "corpus callosum fibers rupture sign" or "hood" sign. Most of the CC fibers in PDD patients had a downward direction, creating a characteristic "hood" sign with depletion of its tractography pattern. The sensitivity of PDD diagnostics using DTT "hood" sign was 88.9%, specificity 77.4%, the diagnostic accuracy of 80%.

Conclusion: Our study using DTT demonstrates that "hood" sign could be a promising biomarker of PDD. We also found that ADC values in the ventral SN can help to discriminate PD patients and healthy subjects.

Disclosure: Nothing to disclose

P2263

Transient global amnesia (TGA). Study of functional connectivity in the memory networks using resting state functional MRI (rsfMRI) during the acute phase

E. Rigal[1], P. Peran[2], B. Lemesle[1], E. Barbeau[3], F. Bonneville[4], J. Pariente[5]

[1]Toulouse Univesrity Hospital, Neurology, [2]INSERM u825, neurologie, [3]Toulouse Univesrity Hospital, Reasearch, [4]CHU Purpan, Neuroradiologie, [5]CHU Purpan, neurologie, Toulouse, France

Background and aims: The transient global amnesia (TGA) is a sudden onset of a anterograde and retrograde amnesia that last up to 24 hours. Use of structural high resolution MRI can detect a focal and selective lesion located on the CA1 part of the hippocampus observed only 72h after onset of the episode (day 3). In this study we investigated a functional impairment during the acute phase of TGA patients. The aim of this study is to identify functional connectivity impairment using resting state functionnal MRI (rsfMRI) and specify cognitive impairment during the acute phase of TGA.

Methods: 11 patients were included during the acute phase of TGA and matched to 14 control subjects at the Toulouse University Hospital. All subjects were evaluated during two successive visits, acute phase and 3 days after (Day 3). At each visit a neuropsychological assessment, and structural MRI and rsfMRI (seed-to-voxel method) were performed.

Results: Impairment of episodic memory ($d=2.89$; $p<0.0001$) and executive functions ($d=1.72$; $p<0.0001$) was observed in acute phase in the atient group. Hippocampal lesion (CA1) was found in all patients at Day3. A reduction in functional connectivity between the hippocampus, the left polar temporal area and the lower left prefrontal gyrus was found during the acute phase of TGA relative to controls ($p=0.001$). No difference with controls was found at day 3 in rsfMRI.

Conclusion: These data suggest that memory impairment observed during the acute phase of TGA correspond to a reversible functional dysconnexion between the medial temporal structures and frontal regions.

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P2264

Recovery of language comprehension in the minimally conscious state studied by FDG-PET

S. Wannez[1], A. Thibaut[1], C. Di Perri[1], G. Vitali Roscini[1], M.-A. Bruno[1], C. Chatelle[1], C. Bernard[2], R. Hustinx[2], P. Maquet[3], S. Majerus[4], S. Laureys[1]

[1]Coma Science Group, Liege, Belgium, [2]University Hospital of Liège, Liege, Belgium, [3]University of Liège, Cyclotron Research Centre, University Hospital of Liège, Liege, Belgium, [4]University of Liège, Departement of Psychology, Cognition and Behaviour, Liege, Belgium

Background and aims: The minimally conscious state (MCS) can be subcategorized in MCS minus (i.e., patients showing non-reflex behaviour such as visual pursuit, localization to pain or to objects or contingent behaviour to emotional stimuli) and MCS plus (i.e., the presence of command following) (1). We here aim to assess changes in brain metabolism related to the recovery of language understanding and command following in severely brain-damaged patients with chronic MCS.

Methods: Brain metabolism was assessed using [18F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) in 32 patients with chronic MCS minus. 5 patients were reassessed by FDG-PET after clinical recovery of language comprehension (i.e., evolved to MCS plus according to Coma Recovery Scale Revised assessments (2)). One patient was excluded because of left-handedness. Demographic data are reported in table 1. Data were pre-processed and analysed by means of statistical parametric mapping (SPM8).

Patient	Age (in years)	Aetiology	Time since injury (in months)	Interval between assessments (in months)
MCS1	57	cardiac arrest	8	17
MCS2	25	traumatic	25	37
MCS3	23	traumatic	10	32
MCS4	38	CVA	62	25

Table 1: Demographic data of severely brain damaged patients in minimally conscious state who recover functional language comprehension.

Results: Compared to age-matched control subjects, patients in MCS minus showed significant hypometabolism in the left dominant hemisphere encompassing the language network (Figure 1). Recovery to MCS plus was paralleled by recovery of metabolism in the right temporo-occipital areas, including hippocampus and parahippocampus (Figure 2).

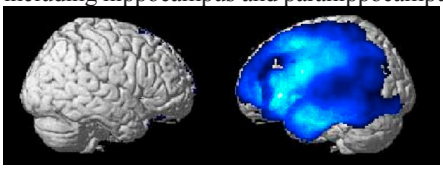


Figure 1: Significant cerebral hypometabolism, as compared to matched controls, in patients with signs of consciousness without language comprehension (i.e., minimally conscious state minus).

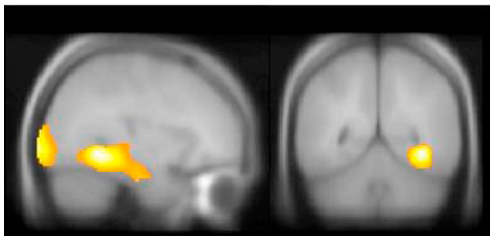


Figure 2: Areas with an increased brain metabolism after recovery of language comprehension and response to command (right temporo-occipital areas, including hippocampus and parahippocampus).

Conclusion: Recovery of language understanding and command following in severe massive left-hemispheric brain-damaged patients with MCS minus seems to correlate with an increase in contralateral right hemispheric metabolic activity rather than in peri-lesional areas as can be observed in aphasia and focal stroke lesions (3). Bruno et al. (2011). Journal of Neurology. Giacino et al. (2004). Archives of Physical Medicine and Rehabilitation. Heiss et al. (2003). Neuroimage.

Disclosure: Nothing to disclose

Neurological manifestations of systemic disease 2

P2265

Brucellosis and inflammatory cerebral lesions: a diagnostic challenge

C. Machado, S. Rocha, J. Cruz Araújo, J. Pinho, E. Lourenço
Braga, Portugal

Background and aims: Human brucellosis remains a common zoonotic infection and Portugal is one of the countries where it is endemic.

Case Report: A 62-year-old man was admitted for a 4-day history of isolated gait distrurbance. Neurological examination revealed right-sided hemiparesis and pyramidal signs. Brain MRI showed a left corona radiata pseudotumoral lesion.Wright agglutination test (WAT) was positive in blood (Brucella abortus 1/640) and negative in CSF. Additional extensive etiological investigation was negative. After a 6-week course of rifampicin and doxycycline, the patient improved and WAT was negative 7 months later.Two years after treatment, the patient was admitted with nausea, vomiting and vertigo for 3 days. Neurological examination revealed right ataxic hemiparesis and right sixth nerve palsy. General physical examination was normal. MRI revealed lesions in the dorsal part of the midbrain and in the superior cerebellar peduncle. WAT was positive (Brucella abortus 1/320) and further complete basic and immunological analysis and serological studies were normal. CSF study showed mildly elevated protein content (0.53g/L), nine white cells and normal glucose; positive unmatched oligoclonal bands and WAT and culture were negative. He started treatment with rifampin, doxycycline and co-trimoxazole. Four months after treatment, he presented clinical improvement, WAT was negative and the MRI lesions were smaller.

Conclusion: There is no consensus in literature regarding diagnostic criteria and treatment for NB. Despite absence of definite confirmation of NB in our patient, exclusion of other etiologies and clinical and imagiological improvement after more prolonged treatment is suggestive of NB.

Disclosure: Nothing to disclose

P2266

Epilepsy and celiac disease

S. Makhlouf, M. Messelmani, E. Mabrouk, I. Bedoui, J. Zaouali, R. Mrissa
Military Hospital of Tunis, Neurology department, Tunis, Tunisia

Background and aims: Celiac disease (CD) is a chronic inflammatory entheropathy of variable severity, induced by the ingestion of dietary gluten . CD may be associated with a number of neurological disorders, and the prevalence of epilepsy is reported to be increased in patients with CD

Case Report: We report the case of a patient with CD associated to epilepsy.

Results: We report the case of a 37-year-old woman,who has 5 years of generalized seizures resistant to antiepileptic treatment. The patient also reported a weight loss associated with a diarrhea. Neurological examination and EEG were normal. Biology has shown signs of malabsorption who were related to celiac disease.The brain MRI was normal. A gluten-free diet has been associated with antiepileptic drugs. The evolution was marked by the control of seizures

Conclusion: A high prevalence of epilepsy has been reported in patients with CD compared with controls .This is from the existence of a currently well defined syndrome involving seizures, parieto-occipital calcifications and celiac disease (CEC). The calcifications could be lacking in 5% of cases because of the early age of diagnosis of CD. Since it is known that some CEC patients with initial normal CT Scan may develop bilateral parieto-occipital calcifications later during the evolution. The institution of gluten-free-diet helps to control the seizures, due to a better absorption of the antiepileptic drug and correction of metabolic disorders. It is important to search for celiac disease when investigating the etiology of epilepsy in refractory patients, because of the potential curability of the disease.

Disclosure: Nothing to disclose

P2267

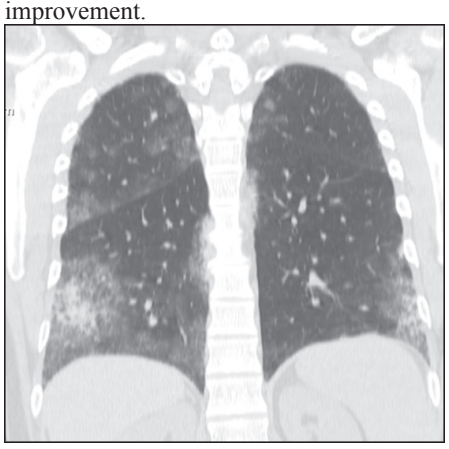
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) – primary or secondary?

S. Moreira[1], L. Ruano[1], J. Roriz[2], C. Veira[2]
[1]Santa Maria da Feira, Portugal, [2]CHEDV, Neurology, Santa Maria da Feira, Portugal

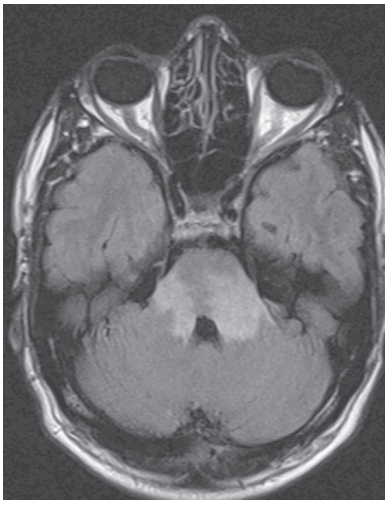
Background and aims: CLIPPERS is an inflammatory CNS disorder of unknown etiology, with characteristic but unspecific radiologic findings and diverse pathological associated findings. It is still a matter of debate whether it represents an independent disorder or a manifestation of an heterogeneous group of diseases.

Methods: Revision of a clinical case.

Results: 39-year-old man, ex-smoker, with a history of granuloma excision from the left foot. Presented with persistent low-fever, malaise, weight loss and symptoms of respiratory tract infection, refractory to several consecutive antibiotics. Thoracic CT showed diffuse interstitial lung infiltrates, with negative bronchial aspirate cultures – initially suggestive of Bronchiolitis Obliterans Organizing Pneumonia (BOOP). Six weeks after initial symptoms, he started complaining of imbalance and right hypoesthesia. Brain MRI revealed T2-hiperintense lesions of the pons and cerebellar peduncles, with discrete local edema and unusual curvilinear patchy gadolinium enhancement – suggestive of CLIPPERS. Blood analysis showed only mild leucocytosis, with negative HIV and self-immunity tests. CSF cytochemical, microbiological and serological analysis was unremarkable. He was discharged with uncertain neurological diagnosis and medicated with corticosteroids, with respiratory improvement but neurological worsening - with left VIth nerve palsy, right central facial palsy, and aggravated ataxia, dysarthria and limb dysmetria. Control MRI showed increased local mass effect and contrast enhancement. Lung biopsy revealed several non-necrotizing granulomatous structures. He was diagnosed with multisystem sarcoidosis and medicated with increased dose of prednisolone (80mg/day), with subsequent neurological improvement.



thoracic CT



T2-weighted brain MRI

Brain MRI gadolinium enhanced

Conclusion: The present case reinforces the idea that CLIPPERS may constitute a neurological manifestation of different systemic diseases, namely sarcoidosis.

Disclosure: Nothing to disclose

P2268

Delay in the diagnosis of acute intermittent porphyria: case presentation.

B. Pelok
Municipal Hospital, Neurology, Odorheiu Secuiesc, Romania

Background and aims: Acute intermittent porphyria is a rare, but underdiagnosed condition, due to its unusual and complex symptomatology.

Case Report: Our 33-year-old female patient was operated at the age of 21 with cerebellar medulloblastoma, followed by radiotherapy and oncologic follow-up, and she was declared in remission after a few years.

From the age of 24, she presented recurrent episodes of abdominal pain, with repeated admissions to medical and surgical wards, including explorative laparoscopy, without positive diagnosis. She developed psychiatric signs in time, i.e. depressive and paranoid elements, for which she was admitted to a number of psychiatric services. A few times she was checked for supposed relapse of the cerebellar tumour by CT-scans of the head.

At the age of 32 she presented progressive, generalized weakness of the limbs, difficulty in walking, and respiratory infections (i.e. pneumonias). The neurological condition was identified as a severe polyneuropathy. The corroboration of clinical data suggested acute intermittent porphyria, confirmed by laboratory findings.

Results: Cessation of psychotropics, administration of hemin-based medicines (outside the country), and carbohydrate-based diet led to a slow recovery in all of her syndromes.

Conclusion: The complex semiology, the apparently unrelated symptoms may delay substantially the diagnosis of acute intermittent porphyria. Usual psychotropic drugs, such as clonazepam, may contribute to the alteration of the clinical picture. In our opinion, the remitted cerebellar tumour is unlikely to have causal relationship with the metabolic disease, but was important in delaying the diagnosis of the later.

Disclosure: Nothing to disclose

P2269

Acute intermittent porphyria: axonal or demyelinating peripheral neuropathy ?

M. Philibert[1], P. Sahuc[2], S. Attarian[1], P. Alla[2]
[1]CHU La TIMONE Marseille, Neurophysiology, Marseilles, France, [2]Army Instruction Hospital Sainte Anne, Toulon, Neurology, Toulon, France

Background and aims: Acute Intermittent Porphyria (AIP) is an autosomal dominant disease due to porphobilinogen (PBG) deaminase enzyme deficiency, characterized by acute life-threatening attacks of non specific neurovisceral symptoms.

Case Report: We report a patient who developed acute tetraplegia due to AIP with electromyography conduction anomalies.

Results: A 20-year-old woman was admitted for acute tetra paresis occurring after a trip on India. She had no medical or familial history and did not use any treatment. Symptoms began with fever, headache, myalgia and abdominal pain without diarrhea. Then, she complained about abdominal pain explored by normal tomography. Her initial examination revealed severe tetraparesis predominantly in proximal limbs that started one week before by lower limbs, facial diplegia, distal lower limbs hypoesthesia, areflexia, tachycardia, abdominal pain and constipation. Paraclinical investigations showed hepatic cytolysis and hyponatremia. Cerebrospinal fluid (CSF) revealed immunoglobulins synthesis without high protein level. Electromyography showed motor and sensory axonal loss associated with conduction blocs and temporal dispersion. Infectious blood analysis and anti ganglioside antibodies were negative. She was diagnosed Guillain Barré syndrome (GBS) and treated by intra-veinous immunoglobulins. She worsened under treatment presenting complete quadriplegia, dyspnea, swallowing difficulties, neuropathic pain in lower limbs, major anxiety and hallucination. EEG revealed fronto-temporal epilepsy; cerebral and spinal MRI were normal. Qualitative urine porphobilinogen and aminolevulinic acid were elevated. She was finally diagnosed with AIP and received Hemin infusions.

Conclusion: AIP must be considered in atypic GBS; especially if associated with abdominal pain, psychiatric symptoms and hyponatremia. We describe a rare case with demyelinating electromyography anomalies.

Disclosure: Nothing to disclose

P2270

Radiological investigations in Takayashu disease with stroke: report of two cases and review of the literature

A. Riahi[1], A. Arous[2], L. Rzigui[3], C. Drissi[2], M. Ben Mahmoud[2], N. Hammami[2], R. Sebai[2], S. Nagi[2], M. Ben Hammouda[2]

[1]Tunis, Tunisia, [2]National Institute of Neurology, Neuroradiology department, Tunis, Tunisia, [3]National Institute of Neurology, Neurology department, Tunis, Tunisia

Background and aims: Takayashu disease (TD) is a chronic inflammatory arteritis of unknown etiology. It affects principally the aorta and its chief branches. Strokes are rare complications in TD. We report here two cases of TD revealed by ischemic stroke in two young women and we discuss its clinical and radiologic features.

Methods: Two women aged 26 and 30 years, respectively, presented with right hemiplegia and aphasia. Both patients had presented upper limbs pulse asymmetry and cervical murmur on auscultation. They underwent brain CT-scan and MRI, angioscanner of supra-aortic vessels and Willis cycle, and echography and Doppler.

Results: Brain imaging showed left middle cerebral artery (MCA) infraction in the first case and left carotidal territory (middle and anterior territories) infraction in the second. Angioscanner exploration of supra-aortic vessels showed a complete thrombosis of the left primitive carotid expanding to the internal carotid and the MCA in the first patient, and 90% stenosis of the left carotid with vertebral arteries occlusion at their origins in the second. Both patients showed a diffuse vessel wall poorly echogenic thickening at echography with hyperemia at Doppler. A complement of thoracoabdominal angioscanner showed abdominal aorta lesions in the first patient. Diagnosis of TD was made according to the Ishikawa criteria. Radiologic criteria are preponderant with 7 out of 13 criteria. Our observation reminds that Doppler-echography and angioscanner are sufficient and can supplement the arteriography. Our patients were put on corticosteroids in addition to anticoagulant treatment.

Conclusion: While stroke represents a rare complication of TD, this diagnosis must be suspected in young women.

Disclosure: Nothing to disclose

P2271

Association between asymmetric dimethylarginine and diabetic neuropathy

Y. Tamam[1], E. Uzar[1], A. Tay[2]

[1]Diyarbakir, Turkey, [2]Diyabakir, Turkey

Background and aims: Asymmetric dimethylarginine (ADMA) as an endothelial nitric oxide synthase inhibitor is an important marker of endothelial dysfunction. There are a few studies focusing on relationshp between blood ADMA and diabetic neuropathy. The aim of this study was to evaluate the relationship between serum ADMA levels among diabetic neuropathy cases

Methods: 141 patients with diabetic neuropathy and 91 healthy subjects were included in the study. All type-2 diabetic patients underwent electrophysiological and neurological examination. Serum ADMA levels were determined by using the ELISA method.

Results: The serum ADMA levels in diabetic neuropathy patients were found to be statistically significantly lower than those of the control group (p=0.005). There were no significant differences among patient groups in terms of disease course, age and sex.

Conclusion: Changes in blood ADMA levels in the diabetic neuropathy patients may be an indicator of oxidative stress and endothelial dysfunction in the pathogenesis of diabetic neuropathy. It could be used as a marker in the severity of diabetic neuropathy.

Disclosure: Nothing to disclose

P2272

Three non-alcoholic Wernicke encephalopathy cases

I. Tatlidil, H. Uluğut Erkoyun, H.S. Türe, T. Kurt İncesu, Y. Secil
Katip Celebi University, Atatürk Training and Research Hospital,, Izmir, Turkey

Background and aims: Wernicke encephalopathy is a medical emergency secondary to thiamine deficiency. Suspicion of diagnosis in patients having remarkable history and clinical symptoms are important. We describe three cases of Wernicke Encephalopathy having non-alcoholic etiology.

Case Reports: Our three cases are male patients aged 49 to 66. All three cases had no history of use of alcohol and all of them had gastrointestinal disease causing impairment of thiamin uptake. Common characteristics of history were impairment of nutrition, history of having total parenteral nutrition, impairment of consciousness state, nausea and vomiting. All three patients had history of hospitalization in internal medicine related clinics. All of them had nystagmus in neurological examination; none of them had classical clinical triad of Wernicke Encephalopathy.

Results: Two of the cases had response to thiamin treatment and two of cases, including the case where thiamin treatment could not be assessed, had typical lesions in Magnetic Resonance Imaging involving brainstem and diencephalon. Finally, all three cases were diagnosed as Wernicke encephalopathy.

Conclusion: Patients having alcoholic background alert the clinician for the diagnosis of Wernicke encephalopathy. However, autopsy series of hospital show most of non-alcoholic Wernicke encephalopathy cases are underdiagnosed. Rarity of presentation of classical clinical triad and limited neurological evaluation due to coma state are the other challenges of diagnosis of Wernicke encephalopathy. All three cases are demonstrative to emphasize the clinical evidence of Wernicke encephalopathy other than alcohol usage.

Disclosure: Nothing to disclose

P2273

Multiple Sclerosis and systemic Behçet syndrome as comorbid disorders

B. Zeydan, U. Uygunoğlu, S. Saip, A. Siva
Istanbul University Cerrahpaşa School of Medicine, Neurology, Istanbul, Turkey

Background and aims: Although it is less frequently seen, Behçet Syndrome (BS) is often included in the differential diagnosis of Multiple Sclerosis (MS). In young individuals with subacute/insidious central nervous system(CNS) symptoms/signs, since neurological presentations have resemblances, CNS involvement of BS, neuro-Behçet's syndrome (NBS) is considered commonly as an alternative to MS. But MS and systemic BS may rarely seen together. The aim of this study is to examine clinical-radiological courses of patients, diagnosed both as MS and BS.

Methods: We retrospectively examined 10 patients (Male:4/Female:6) with both MS and BS, who attended our clinical neuroimmunology and MS clinic between 1994 and 2014.

Results: BS and MS mean ages at time of diagnosis are 30.4±8.7 and 33.3±9.9 respectively. All patients had systemic involvement (such as mucocutaneus, eye, musculoskeletal), which is essential for BS, whereas in MS it is atypical. All patients had typical MS lesions (all patients: supratentorial periventricular-subcortical-juxtacortical lesions, 5 patients: spinal cord lesions, 1 patient: small brainstem and cerebellar lesions, 1 patient: optic nerve involvement), while 2 patients also had a history of large diencephalic/brainstem lesions, which are characteristic of NBS. In 3 of 5 patients with cerebrospinal fluid examination performed, oligoclonal bands were positive and 4 of them had neutrophilic pleocytosis. Follow-up duration is 7±6.6 years and the last EDSS is 1.7±2.3.

Conclusion: Both NBS and MS have distinctive features and they are unlikely to be confused when clinical, radiological and cerebrospinal fluid analysis evaluated carefully. However MS and systemic BS may rarely seen together as comorbid disorders.

Disclosure: Nothing to disclose

Neuro-oncology; neurotoxicology/ occupational neurology

P2274

Cisplatin inhibits the expression and transport of mitochondrial dynamic factors in mice

I. Bobylev[1], A. Joshi[1], M. Barham[2], W. Neiss[2], H.C. Lehmann[1]

[1]University Hospital of Cologne, Neurology, Cologne, Germany, [2]University of Cologne, Department of Anatomy I, Cologne, Germany

Background and aims: Sensory neuropathy is a common adverse effect of the antineoplastic agent cisplatin. There is increasing experimental evidence that dysfunctional mitochondria play a crucial role for the development of cisplatin induced neuropathy. We explored the role of axonal mitochondria in a murine model of cisplatin induced sensory neuropathy.

Methods: We assessed the morphology and function of axonal mitochondria in different models of cisplatin induced neuropathy including transgenic mice with cyan fluorescent protein labeled mitochondria. Neuropathy was assessed by nerve conduction studies, electron microscopic and histological analysis of distal nerve segments and skin sections. In addition, we determined mRNA transport of nuclear encoded mitochondrial proteins in axons.

Results: We found that high doses of cisplatin induced neuropathic changes primarily affecting sensory fibres. These morphological changes were accompanied by mitochondrial damage as revealed by electron microscopy. In addition we found an impaired expression and axonal transport of nuclear encoded mitochondrial fusion / fission GTPases that correlated with the degree of mitochondrial damage.

Conclusion: Our results support the notion that the dynamics of axonal mitochondria are affected by systemic cisplatin treatment.

Disclosure: Nothing to disclose

P2275

Primary intracranial Rosai-Dorfman disease (RDD) mimicking meningiomatosis

L. Boccara Girardstein[1], J. Capron[1], F. Bielle[1], M. Peyre[2], N. Martin-Duverneuil[1], K. Hoang-Xuan[1], A. Idbaih[1]

[1]1-APHP, Groupe Hospitalier Pitié-Salpêtrière,Paris, France. [2]-2Institut du Cerveau et de la Moelle épinière (ICM), INSERM U 1127, CNRS, UMR 7225, Paris, France. 3-UPMC University Paris 6, UM 75, Paris, France., Service de Neurologie 2 , Paris, France, 2GH Pitié-Salpétrière, Neurochirurgie, Paris, France

Background and aims: Rosai-Dorfman is a rare non Langerhans histiocytosis occurring in young adults. It is a multisystemic disease mainly affecting cervical lymph nodes. Extranodal sites include skin, orbits, upper respiratory tract, testes and central nervous system (CNS). CNS involvement is rare, reported in 5% of cases. Histological and immunochemical examination show, in one hand, infiltration of histiocytes, lymphocyte and plasma cells and in the other hand, a typical emperipolesis.

Case Report: We present the case of a 39-year-old man who presented with partial epileptic seizures and right-sided headaches. Brain MRI showed multiple extra-axial lesions at the skull convexity mimicking diffuse nodular pachymeningitis or diffuse meningiomatosis. Meningeal lesions induced mass effect on brain structures and important oedema within the contiguous brain parenchyma on T2-weighted images. After contrast infusion, the lesions were homogeneously and strongly enhanced.

No systemic lesions or inflammation were detected on PET scan and on blood examinations.

Results: The pathological examination, after surgical biopsy, revealed S100+/CD68+/CD1a- histiocytes, lymphocytes, plasma cells and emperipolesis, in favour of RDD.

Conclusion: Although it is rare, primary intracranial RDD disease should be discussed faced to meningioma-like, meningiomatosis-like or pachymeningitis-like isolated lesions.

Disclosure: Nothing to disclose

P2276

From Trousseau syndrome to CoaGlio IV: the translational journey from our patients via glioblastoma biology back to a randomized, controlled multicenter trial

S. Kuhn[1], T. Kratzsch[2], L. Handel[3], R. Kalff[3], U.-K. Hanisch[4], P. Vajkoczy[2]

[1]Potsdam, Germany, [2]Charité - Universitätsmedizin Berlin, Neurosurgery, Berlin, Germany, [3]University Hospital Jena, Neurosurgery, Jena, Germany, [4]Universitätsmedizin Göttingen, Neuropathology, Göttingen, Germany

Background and aims: Venous thromboembolism (VTE) is a paraneoplastic monitor of aggressive glioblastomas. Prophylaxis could not only prevent VTE, but could generate additional anti-tumor therapy.

Methods: Clinical file review, prospective cohort study, tumor immunohistochemistry, cell assays, and animal models were performed. Target for VTE prevention was identified. Clinical study protocol for anticoagulation was developed.

Results: One third of patients experience VTE. They show activated coagulation factors II-XII in their circulation. Those with VTE show correlation with multiple factor dysregulations ($p=0.018$). Further, patients with preoperative co-activation of antithrombin III survive longer; patients with normal or low antithrombin III survive shorter. Glioblastoma tissue expresses all coagulation factors of the intrinsic as well as the common final pathway ($p<0.05$), and the coagulation factor receptors PAR-1/PAR-4 ($p<0.05$). The activation of receptors with increases DNA synthesis, proliferation, and migration ($p<0.05$). Thrombin and PAR-1 inhibitors, like hirudin, unfractionated heparin, antithrombin III, PPACK, low molecular weight heparins, and the PAR-1 specific antagonist FLLRN inhibit proliferation of tumor cells ($p<0.01$). Consequently, VTE prophylaxis by LMWH reduces sizes of human glioblastomas in xenografts ($p<0.05$). The randomized, controlled, multinational CoaGlio-IV trial includes operated patients from their first postoperative day to receive the factor Xa inhibitor apixaban for a 12-month-period accompanying standard treatment. FXa inhibition should not only prevent VTE and related short-term deaths, but also should improve long-term prognosis by tumor inhibition.

Conclusion: Transfer of symptoms into the lab and translation back into clinical trials is necessary, as VTE is a dangerous complication, and glioblastoma is still a deadly disease.

Disclosure: Nothing to disclose

P2277

Brainstem gliomas in adult patients.

J.R.L.D.M. Marques[1], M. Fernandes[1], J. Passos[1], A.L. Azevedo[1], I. Costa[1], J.M.D.A. Nunes[1], T. Pimentel[2], D.M.C. Salgado[1], J.M.T.B. Marques[1]

[1]Instituto Português de Oncologia de Lisboa, Neurology, Lisbon, Portugal, [2]Instituto Português de Oncologia de Lisboa, Lisbon, Portugal

Background and aims: Brainstem gliomas are uncommon in adults (only 1%–2% of intracranial gliomas), representing nonetheless a very heterogeneous oncological entity. Although the clinical, imaging and prognosis of brainstem gliomas is well characterized in children, in the adult population it has not been as thoroughly evaluated.

Methods: Demographic, clinical, treatment and survival characterization of adult patients with brainstem glioma (histological and/or clinical-radiological diagnosis). Medical charts from patients followed between 1998 and 2012 in a Portuguese oncological hospital were reviewed.

Results: 22 patients were included, 10 female patients, mean age at diagnosis 33.5±9.4 years. The mean time to diagnosis was 10.3 months. The most common earlier symptoms/signs were cranial nerve dysfunction (17), motor dysfunction (8) or ataxia (5). On imaging (MRI), brainstem gliomas were classified as diffuse intrinsic in 17 patients, cystic/necrotic in 2 and exophytic in 3. There was gadolinium-enhancement in 7 patients. Only ten patients were biopsied (open or stereotactic biopsy): 6 of them were diffuse tumors, 2 were cystic/necrotic and 2 were exophytic. Histological diagnosis were varied: pylocytic astrocytoma (1); grade II (3) and grade III (3) astrocytomas; glioblastoma (1); grade II (1) and grade III (1) oligodendrogliomas. All but one patient were treated with radiotherapy; 17 patients were also treated with chemotherapy. There were 11 deaths; 4 patients were lost to follow-up.

Conclusion: Our series is similar to previous studies in adult patients with brainstem gliomas, documenting a marked clinical and radiological heterogeneity. We highlight the importance of a histological diagnosis in this rare tumor, with important implications in treatment and prognosis.

Disclosure: Nothing to disclose

P2278

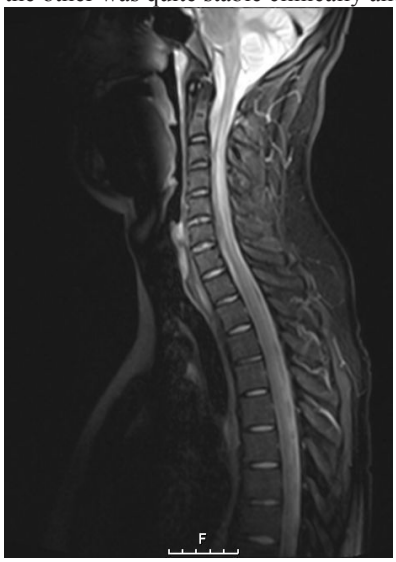
Nitrous oxide recreational use and subacute combined degeneration

A. Papathanasiou[1], T. Ham[1], T. Cope[1], S. Chawda[2], A. Chaudhuri[1]

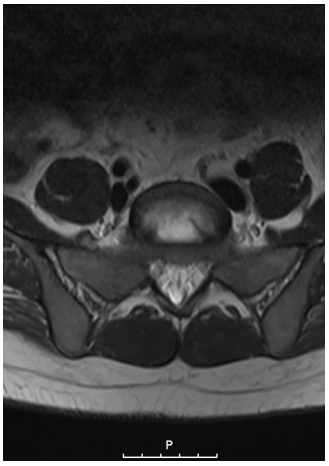
[1]Department of Neurology, Essex Centre for Neurological Sciences, Queen's Hospital, Romford, UK, Neurology, London, United Kingdom, [2]Department of Radiology, Essex Centre for Neurological Sciences, Queen's Hospital, Romford, UK, Radiology, London, United Kingdom

Background and aims: Nitrous oxide is a widely used anaesthetic gas though also recreationally misused quite commonly. It is a potential neurotoxic agent due to functional disruption of cobalamin (vit B12), which serves as an active cofactor for methionine synthase, a critical enzyme in the methylation of myelin sheath phospholipids.

Methods: We report two cases of young males, presented with subacute onset and progressive course of gait difficulties. On examination both had spastic paraparesis and proprioception deficits resulting in spasticoataxic gait. One patient had significant low vitamin B12 (160 ng/l), while the other had borderline (248ng/l). Both reported recreational use of nitrous oxide for couple of years. MRI on both cases revealed hyperintense signal in the posterior columns of cervical spine. Intramuscular injections of B12 were commenced and after 6 months one patient was significantly improved with corresponding improvement on MRI, while the other was quite stable clinically and radiologically.



Saggital STIR cord MR image demonstrates hyperintense signal in the cervical spine



Axial MR image of cervical spine level demonstrates hyperintense signal

Conclusion: Nitrous oxide or laughing gas has been increasingly misused for recreational purposes, due to its wide commercial availability, causing subacute combined degeneration. Low or borderline levels of vitamin B12 can be found, therefore it is useful to measure methylmalonic acid and homocysteine levels to detect early B12 deficiency. Edema secondary to demyelination and eventual gliosis result in the typical MR findings of increased T2 signal in the dorsal and to a lesser extend in lateral and anterior columns of the cervical and occasionally thoracic cord. Functional recovery is variable and difficult to predict in relation to serum vitamin B12 levels.

Disclosure: Nothing to disclose

P2279
Guillain-Barré syndrome induced by platin-based chemotherapy

B. Herlin[1], E. Pappa[2], D. Ricard[2], T. Lenglet[3], T. Maisonobe[1], D. Psimaras[4]
[1]Pitié-Salpêtrière, Paris, France, [2]Paris, France, [3]Pitié-Salpêtrière Hospital, Service Explorations Fonctionnelle Neurologie, Paris, France, [4]University René Descartes, Department of Neurology Mazarin, Hôpital Pitié-Salpêtrière, Paris, France

Background and aims: Platin-based chemotherapy has essentially been associated with acute neuro-muscular hyperexcitability and a sensory axonal delayed dose-related neuropathy. We report a series of patients presenting Guillain-Barré Syndrome (GBS) short after the administration of platin analogs for a solid tumor treatment.

Methods: Our 4 patients, 1 man and 3 women, aged from 53 to 62 years, were treated for various carcinomas and developed symptoms of GBS (3 demyelinating and 1 axonal form) starting a few days after chemotherapy (2 to 7 days). None of our patients had any history or paraclinical examination evoking usual causes of GBS.

Results: All patients had a complete clinical recovery after an intravenous immunoglobulines (IVIg) treatment.

Conclusion: Guillain-Barré syndrome is classically associated with hematological malignancies and only rarely with solid tumours, with the exception of paraneoplastic conditions or induced by chemotherapy. To date, only platinum analogues have been associated with GBS, as it is the case with our patients. We propose that it is important to establish if the development of GBS is a consequence of platinum analogues in order to suspend chemotherapy treatment and propose IVIg therapy.

Disclosure: Nothing to disclose

P2280
Abstract cancelled

P2281
Evaluation of relationship between overactive bladder syndrome and use of antidepressant drugs in female patients

S. Albayrak[1], V. Solmaz[2], Y. Gecten[3], D. Aksoy[4], M.C. Nacar[5], F. Erdemir[3]
[1]Bozok unıversty medical faculty, urology, yozgat, Turkey, [2]Turkey, Turkey, [3]Gazıosmanpasa unıversty medical faculty, urology, Tokat, Turkey, [4]Tokat, Turkey, [5]Tokay state hospital, obstretric and gynecology, tokat, Turkey

Background and aims: Overactive bladder (OAB) is defined by the International Continence Society as a symptom complex of urinary urgency, generally accompanied by frequency and nocturia with (OAB wet) or without (OAB dry) urinary urgency incontinence (UUI). The objective of this study was to investigate the relationship between OAB and use of antidepressant in women.

Methods: Of the 205 women who were invited, patients were then divided into two groups: group 1: 113 patients with use of antidepressant due to various cases and group 2: 92 healthy controls. Patients were performed OAB-V8 questionnaire. In order to collect clinical and demographic variables, a medical history was conducted with questions regarding age, weight, and height, number of pregnancies. In the present study we compared women using antidepressants and healthy control group according to prevalence of OAB. Prevalence of OAB between two groups was compared. İn addition prevalence of OAB was compared also according to antidepressant types

Results: The mean age of the attendees was 38 years (range 25-82). In groups demographic datas were similar. In correlation analysis of datas ICIQ-SF, BDI scores, and patient age was positively correlated with OAB-V8 ($r=0.379^{**}$, $r=0.318^{**}$, $r=0.247^{**}$) (respectively). Patient age, and BDI scores was positively correlated with ICIQ-SF ($r=0.187^{**}$, $r=0.129^{*}$) (respectively) ($^{*}p<0.05$, $^{**}p<0.01$). Results are shown in Table 1. The highest prevalence in group of fluoxetine (63.6%), and lowest prevalence in group of sertraline was determined. Likewise this difference was statistically significant between the antidepressant groups (P=0.038).

Conclusion: In current study we found that overactive bladder syndrome was associated with the use of antidepressant.

Disclosure: Nothing to disclose

P2282

The role of mTOR and PI3K/Akt in the pathogenesis of different types of gliomas

S. Szlufik[1], W. Grajkowska[2], D. Perek[3], B. Dembowska-Bagińska[3], I. Filipek[3], P. Daszkiewicz[4], M. Sidor[1], J. Jozwiak[1]

[1]Center for Biostructure Research, Medical University of Warsaw, Department of Histology and Embryology, Warsaw, Poland, [2]The Children's Memorial Health Institute, Department of Pathology, Warsaw, Poland, [3]The Children's Memorial Health Institute, Department of Oncology, Warsaw, Poland, [4]The Children's Memorial Health Institute, Department of Neurosurgery, Warsaw, Poland

Background and aims: The most frequent molecular alterations found in different types of gliomas belong to two groups of signaling proteins: cell cycle and the growth factor-regulated signaling pathways. The aim of this study was to detect changes in expression of the tumour suppressor PTEN, and the phosporylated forms of mTOR and PI3K/Akt pathway, which may lead to the formation of gliomas.

Methods: To characterize hyperactivation of mTOR and PI3K/Akt pathway in gliomas, we analyzed astrocytoma, oligodendroglioma and mixed glioma tissue samples from 50 patients operated in the Department of Neurosurgery of the Childrens' Memorial Health Institute. Monoclonal antibodies against pAkt, PI3K, PTEN, pS6, pMTOR, pErk, pMek, pRSK1, PRAS40 were used and detected by standard Western Blot method.

Results: We detected hyperactivation of phosphorylated mTOR, Erk and Akt in the majority of glioma samples (90%). The expression of pS6, pMek, pRSK1 was found in roughly the same proportion. We also observed an insignificant overexpression of pPRAS40. PTEN was not found in most of astrocytomas, especially in higher-grade tumours.

Conclusion: Gliomas are genetically complex tumours. In the majority of gliomas, mTOR and PI3K/Akt pathways are hyperactivated, while the activity of tumor suppressor PTEN is decreased. Loss of PTEN function can lead to hyperactivation of Akt, which promotes phosphorylation of other particular proteins of Akt/mTOR pathway, like p70 S6 kinase or S6 protein. This co-activation of mTOR and PI3K/Akt pathways can play an important role in the proliferation and differentiation of low- and high-grade gliomas.

Disclosure: Nothing to disclose

Spinal cord and root disorders 1

P2283

Paraplegia after spinal anesthesia due to adhesive arachnoiditis

R. Barbosa, F. Ladeira, L. Alves, F. Sá, E. Medeiros
Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Neurology Department, Lisbon, Portugal

Background and aims: Acute flaccid paraparesis following spinal anesthesia is a rare neurological complication and multiple causes need to be considered. Direct effects of topic anaesthetics can be responsible through a neurotoxic reaction leading to axonal degeneration of nerve roots or by inducing a leptomeningeal inflammatory reaction with subsequent adhesive arachnoiditis.

Case Report: An 88-year-old woman who underwent hemiarthroplasty of left femoral head under spinal anesthesia with levobupivacaine two days earlier, develops back pain and acute paraplegia. On neurologic examination she had flaccid paraplegia, lower limb hyporeflexia and asymmetric hyposthesia with T12 and L1 level (right and left respectively), apalesthesia and impairment of position sense on the lower limbs, urinary and fecal incontinence. Dorsolumbo-sacral MRI showed conglomeration of cauda equine roots with gadolinium enhancement, compatible with arachnoiditis, and degenerative alterations of the lumbar canal. Electromyography (EMG) revealed absence of sensitive and motor action potentials in the lower limbs. We assumed chemical arachnoiditis and started two, 3-day long cycles of IV methylprednisolone as well as physiotherapy without improvement. She was discharged 2 months later, without any change in the admission neurological exam. She has a urinary catheter and uses a wheel chair. A new EMG, three months later showed, additionally, fibrillation potentials in the lower limbs.

Conclusion: Close temporal relation between the onset of the neurologic deficits and spinal anesthesia and suggestive MRI findings allowed the diagnosis of arachnoiditis by local anesthetic neurotoxicity. Although not yet proved, a stenotic spinal canal appears to be a risk factor for this complication.

Disclosure: Nothing to disclose

P2284

Idiopathic spinal cord herniation

Y. Beckmann[1], F. Gelal[2], N. Gürgör[3], G. Güvenç[4]
[1]Izmir, Turkey, [2]Katip Çelebi University Atatürk Research and Training Hospital, Radiology, Izmir, Turkey, [3]Katip Çelebi University Atatürk Training and Research Hospital, , Neurology, Izmir, Turkey, [4]Katip Çelebi University Atatürk Training and Research Hospital, Neurosurgery, Izmir, Turkey

Background and aims: Dorsal herniation of the spinal cord through the dura is a very uncommon phenomenon that results in progressive myelopathy. Idiopathic spinal cord herniation is not usually recognized in neurology practice. Although it is a treatable condition, misdiagnosis and delayed diagnosis remain a major concern. We report two cases with idiopathic spinal cord herniation who had full recovery after the surgery.

Case Report: A 62-year-old previously well male presented with progressive spastic paraparesis that was exacerbated by walking for 5 years. He was diagnosed as having transverse myelitis and treated by corticosteroids at a different institution. His symptoms persisted. A 58-year-old previously well male presented with a 3-year history of thoracic back pain and spastic progressive paraparesis.

Results: Imaging revealed a dorsal dural defect with herniation of the spinal cord at T7 in both cases (Figur 1). The patients underwent a T7-T8 laminoplasty to repair the dural defect (Figure2). At 1-year follow-up, both patients noted a significant improvement in strength and back spasticity.

preoperative spinal cord herniation

postoperative spinal cord herniation

Conclusion: Misdiagnosis is reported in a number of spinal cord herniation case reports. MRI is the investigation of choice for the diagnosis of spinal cord herniation. Sagittal sections often demonstrate enlargement of the dorsal subarachnoid space, with ventral displacement of the thoracic spinal cord. On axial imaging, the cord herniation is attached to the anterior dura mater. Treatment consists of either conservative management or surgery, but owing to the unclear natural history of the condition. Surgery is generally recommended for patients with motor function deficit or progressive neurological symptoms.
Disclosure: Nothing to disclose

P2285
Abstract cancelled

P2286
Progressive weakness of lower limbs - a case of tuberculous radiculomyelitis

I.-H. Ciorıceanu[1], M.R. Mărceanu[1], R.D. Ionescu[2], D.M. Gabor[3]
[1]Psychiatry and Neurology Hospital, Brasov, Romania, [2]Infectious Diseases Hospital, Brasov, Romania, [3]County Pneumology Hospital, Brasov, Romania

Background and aims: Intramedullary involvement of Mycobacterium tuberculosis (MT) is a rare condition and may be present as a transverse myelitis, radiculomyelitis or pial arteritis with spinal cord infarction and the diagnosis can be neglect and difficult.
Case Report: We present a case of a 78-year-old male admitted with a history of urinary retention, singultus and acute-onset progressive weakness of right lower limb for the past 7 days. He had no history of trauma, fever, back or root pain. A detailed neurological examination was made with evaluation of the motor, sensory and sphincter systems. The next days, his condition continues to deteriorate and the patient develops flaccid paraplegia, despite receiving intravenous corticosteroids treatment.
Results: The involvement of MT was suspected after we excluded other known causes of radiculomyelopathy. Cerebrospinal fluid (CSF) examination revealed high protein content based on Pandy's reaction, elevated level of glucose, positive Polymerase Chain Reaction (PCR) for MT and isoniazid resistance based on Genotype Mycobacteria Direct Test. Magnetic Resonance Imaging (MRI) of the spine revealed altered cervical, thoracic and lumbar medullar signal intensity appearing isointense on T1W and hyperintense on T2W images, no swelling and with leptomeningeal enhancement.
Conclusion: Following the result of the CSF and the MRI of the spinal cord we initiated combined antituberculous treatment and the patient neurological condition gradually improved over the next 10 months, almost with full recovery. Despite it is a rare etiological agent for spinal cord infections, MT must be considered even if we deal with a negative contact or manifest disease in anamnesis.
Disclosure: Nothing to disclose

P2287
Abstract cancelled

P2288

Back pain and radiculopathy secondary to Intracranial Hypertension Syndrome (IHS)

N. Giraldo Restrepo[1], A. Hernandez[2], A. Lopez Garcis[1], J.J. Bravo[1], A. Parralo[2], C. Valencia Guadalajara[1], S. Carrasco García de León[3]

[1]Ciudad Real, Spain, [2]University General Hospital of Ciudad Real, Neurology, Ciudad Real, Spain, [3]Hospital General, Neurology, Ciudad Real, Spain

Background and aims: HIS is typically characterized by headache, vomiting, visual disturbance, diplopia, tinnitus and hearing loss. Moreover, associated back pain and radiculopathy have been scarcely reported in the literature. We present three cases with lumbar symptomatology related to IHS caused by different etiologies.

Methods: Case 1: A 70-year-old female, with headache, vomiting, bilateral papilledema, hearing loss, arterial hypertension, drowsiness and severe back pain. Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) showed triventricular hydrocephalus.

Case 2: A 19-year-old male with history of familiar spastic paraparesis, presented with headache, vomiting, ophthalmoparesis, visual loss, papilledema, and worsening of tetraparesis, areflexia, radicular and back pain. Brain CT and MRI were normal. Electrodiagnostic testing revealed acute radicular affectation.

Case 3: A 70-year-old female, with headache, ophthalmoparesis, blindness, papilledema, tetraparesis and areflexia. CT and MRI showed hydrocephalus. Spinal MRI was normal. Severe acute multiradicular affectation was diagnosed by electrodiagnostic tests.

Results: In all cases the opening pressure of CSF was very elevated (60, 50, and up to 100cm H2O, respectively). CSF in case 3 showed hypoglycorrhachia and malignant cells. Lumbar symptoms improved after CSF shunt, including back pain in case 3 (with meningeal carcinomatosis).

Conclusion: It has been described that back pain associated with HIS may be present in half of cases, and may associate paresis and hypoesthesia that improve after CSF derivation. The main challenge in differential diagnosis could be Guillain Barré syndrome with papilledema. We remark that back pain and radiculopathy can be distracting symptoms evaluating patients with IHS.

Disclosure: Nothing to disclose

P2289

Endovascular treatment for dural arteriovenous fistula – clinical experience

A. Bazina[1], Z. Hucika[2], A. Mišmaš[1], M. Krbot Skoric[1], D. Ozretić[3], Z. Poljaković[4]

[1]Zagreb, Croatia, [2]Zabok, Croatia, [3]Zagreb University Hospital Centre, Department of Diagnostic and Interventional Radiology, Zagreb, Croatia, [4]Zagreb University Hospital Centre, Neurology, Zagreb, Croatia

Background and aims: The aim of this study was to evaluate clinical improvement after endovascular treatment in patients with spinal dural arteriovenous fistula (dAVF).

Methods: We reviewed data on 26 patients with spinal dAVF referred for endovascular treatment to University Hospital Centre Zagreb, University Department of Neurology in a period between August 2008 and June 2014

Results: Study included 26 patients; 18 (69.2%) males and 8 (3.8%) females; mean age 56.29±12.14. History of minor back trauma was positive in 6 (23.1%) patients. The dAVF were localized in cervical 3 (11.54%), thoracic 15 (57.7%), thoraco-lumbar 7 (26.92%) and 1 (3.84%) in sacral level. The most common presenting symptom was paraparesis 18 (69.2%). In 23 (88.46%) patients endovascular treatment was possible, while 3 (11.54%) patients were referred for neurosurgical procedure after spinal digital subtraction angiography. Second endovascular procedure was indicated in 7 (30.43%) patients, while 2 (8.7%) patients who were treated with two endovascular procedures were finally referred for neurosurgical procedure. Among patients who were endovascularly treated 15 (65.22%) showed clinical improvement.

Conclusion: Endovascular treatment for dAVF can be successful as a primary treatment for the majority of patients with this pathology.

Disclosure: Nothing to disclose

P2290

Acute flaccid paralysis subsequent to acute aortoliac occlusion: a case report

O. Jugurt, S. Plesca, M. Sangheli, I. Andronati
INN, Neurology, Chisinau, Moldova

Background and aims: Acute flaccid paralysis is a clinical syndrome with a broad array of potential etiologies, infrequently occurred after ischemic pathology of the spinal cord. Spinal cord ischemia has been reported after thoracic and abdominal aorta surgery, and rarely after interruption of the cord blood supply by embolism at the aortic bifurcation (saddle embolus). Acute aortoiliac occlusion (AAO) is a catastrophic event with high incidence of neurological complications and it is frequently accompanied by myocardial dysfunction.

Case Report: We report a case of a 57-year-old man who developed severe back pain with acute lower extremities paralysis, coldness and pallor in the lower limb (march 2014). There was no weakness in the upper extremities, sphincter muscles of bladder and bowel. His past medical history included a myocardial infarct (2007).

Results: A CT-angiography revealed a segmental occlusion of the distal infrarenal aorta and bilateral common iliac arteries. The transthoracic echocardiography demonstrated a left ventricular aneurysm with mural thrombus, which was the source of this acute spinal cord ischemia. The patient underwent aorto-bifemoral by-pass surgery. Despite this intervention, the paralysis persisted.

Conclusion: Sudden onset of flaccid paralysis should immediately alert the physician, because this cardinal symptom can denote an AAO. This case highligts that AAO needs early recognition, prompt diagnosis and immediate intervention.

Disclosure: Nothing to disclose

P2291

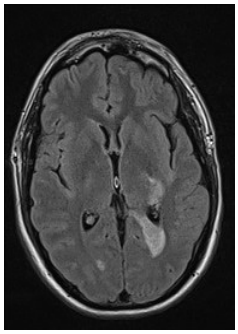
Hyperacute presentation of encephalomyelitis 10 days after onset of mycoplasma pneumoniae infection

V. Keereman, A. Meurs, J. De Bleecker
Ghent University Hospital, Neurology, Ghent, Belgium

Background and aims: Mycoplasma-associated encephalomyelitis is a known entity. The pathophysiological basis is not well understood, but either neurotoxic or autoimmune reactions, or direct invasion of the CNS by the organism are suspected.

Case Report: A 29-year-old male presented to the emergency department, with rapidly ascending paralysis. At the time of presentation, there was tetraplegia, a global sensory level at C5, complete areflexia and increasing respiratory distress. He experienced paresthesias in both arms from 12 hours before, but leg symptoms had only started 2 hours before. Approximately 10 days before, he experienced bronchitis for 1 week. After examination, the patient was sedated and intubated.

Results: Cerebrospinal fluid showed 900 leukocytes/μL and a total protein of 373 mg/dL. Treatment was started with IV corticosteroids, immunoglobulin, acyclovir, ceftriaxone and doxycycline. MRI showed a T2 hyperintense myelum from the conus medullaris to the pons and bilateral supratentorial FLAIR hyperintense white matter lesions. A positive PCR for M. pneumoniae in pulmonary aspirate confirmed an active pulmonary infection. Cerebrospinal fluid M. pneumoniae PCR was negative. After stopping sedation, the patient was conscious and respirator-dependent, with tetraplegia and paralysis of the tongue and inferior division of the facial nerve. After 3 months, he showed limited recuperation and remained completely respirator-dependent. MRI after 1 month showed reduced intracerebral lesions but spontaneous T1 hyperintense signal in the spinal cord, indicating hemorraghic transformation.



Brain FLAIR image on the day after admission showing bilateral hyperintense white matter lesions.

Full spine T2w MRI on the day after admission showing hyperintense T2w signal in the entire spinal cord up to the pons, most extensively in the lower cervical cord.

Full spine T2w MRI on the day after admission showing hyperintense T2w signal in the entire spinal cord up to the pons, most expressively in the lower cervical cord. Cervical and thoracic spine T1w MRI one month after admission

Conclusion: This patient presented with a hyperacute encephalomyelitis, probably due to a dramatic immune response to a M. pneumoniae infection. Intrathecal infection with M. pneumoniae is unlikely, as the CSF PCR was negative.
Disclosure: Nothing to disclose

P2292

Cervical spondylotic myelopathy causing cerebellar type subacute ataxia

A.D. Magalhães[1], M. Oliveira Santos[1], L.P. Faria de Abreu[1], J. Teixeira[2], N. Simas[2], M. Coelho[1]
[1]Hospital de Santa Maria, Neurology Department, Lisbon, Portugal, [2]Hospital de Santa Maria, Neurosurgery Department, Lisbon, Portugal

Background and aims: Classically, cervical spondylotic myelopathy (CSM) causes motor weakness, sensory loss, sensory ataxia, spasticity, increased deep tendon reflexes, extensor plantar response and dynamic Hoffman sign. On the other hand, it is not a common cause of cerebellar type ataxia.
Case Report: An 81-year-old diabetic male was admitted for imbalance and numb and clumsy hands. On neurological examination there was normal muscle tone, predominantly distal limb tetraparesis, weak upper limb deep tendon reflexes, left patellar reflex with contralateral response, absent Achilles reflex, flexor plantar reflex, mild decreased vibration sense up to the knee level, maintained joint position sense, dysmetria on nose-finger and heel-knee-shin tests, intention tremor, truncal ataxia, inability to stand unaided with multidirectional oscillations, widened base, unstable gait and inability to tandem walk.
Results: Brain MRI was unremarkable, CSF analysis showed elevated protein level, anti-neuronal antibodies were negative, detection EMG showed minor demyelinating sensorimotor polyneuropathy and chronic neurogenic right C5 and bilateral C6-C7-C8-D1 lesions due to radiculopathy. Cervical spine MRI showed spinal stenosis of the C3-C6 vertebral level cervical canal with marked spinal cord compression on C3-C4 level. The patient underwent C3-C6 decompressive laminectomy with marked progressive improvement with autonomous walking without ataxia after 1 month.
Conclusion: Despite the minor vibration sense deficit, the patient's severe ataxia was of cerebellar type. We propose that, in rare cases, cervical spondylotic myelopathy can cause ataxia of cerebellar type due to compression of the spinocerebellar tracts.
Disclosure: Nothing to disclose

Monday, June 22 2015
Cerebrovascular diseases 5

P3101
Hemodynamic changes after successful stent retrievers' thrombectomy in acute stroke: a sign of vessel wall injury?

F. Perren[1], J.-M. Pignat[2], V. Mendes Pereira[3]
[1]Geneva, Switzerland, [2]CHUV, University Hospital , Neurology, Lausanne, Switzerland, [3]University of Toronto University Health Network, Interventional Neuroradiology, Toronto, Canada

Background and aims: Stent retrievers with rapid recanalization and acceptable safety have revolutionized intracranial endovascular treatment of acute ischemic stroke. However, animal studies showed that mechanical thrombectomy may cause endothelial injury leading to myointimal hyperplasia. Using transcranial duplex sonography (TDS) monitoring, we observed post-procedural hemodynamic changes in the treated vessel.
Methods: We studied acute ischemic stroke patients with single large intracranial artery occlusion in whom mechanical thrombectomy using stent retrievers was performed. Only those with complete vessel recanalization (modified TICI 2b or 3) as assessed by post-procedural DSA and MRA and in whom early control TDS was performed were retained. Patients treated with intra-arterial thrombolysis or stenting were excluded.
Results: In 28 patients (26 MCA, 2 BA), post acute MRA confirmed complete recanalization without residual stenosis or vasospasm. However, in 24 (17 men; mean age 66.8 yrs) of them TDS (mean 3.4 days after thrombectomy) showed very segmental acceleration of blood flow velocities in the affected arteries (MCA PSVmax at least > 35%) as compared with the contralateral side at same depth; BA PSVmax > 40% as compared to velocities measured in the same vessel). None showed clinical deterioration. Follow-up TDS (mean 20 days) showed normalization in 11/14.
Conclusion: This is the first TDS study showing focal acceleration of blood flow velocities after stent retrievers' thrombectomy. Without residual stenosis, thrombosis or vasospasms, this may be a sign of intimal injury in humans. Whether this is due to local inflammatory agents, neothrombosis or myointimal hyperplasia is yet not clear.
Disclosure: Nothing to disclose

P3102
Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages

N. Raposo[1], M. Planton[1], P. Péran[1], P. Payoux[1], F. Bonneville[1], A. Lyoubi[2], J.-F. Albucher[1], B. Acket[1], A.S. Salabert[1], J.M. Olivot[1], A. Hitzel[1], F. Chollet[1], J. Pariente[1]
[1]TOULOUSE, France, [2]CHU, neurologie, Paris, France

Background and aims: Several studies have suggested that positron emission tomography (PET) amyloid imaging could help to diagnose cerebral amyloid angiopathy (CAA). We investigated the yield of florbetapir, a PET amyloid ligand, for the diagnosis of CAA among patients with intracerebral hemorrhage (ICH).
Methods: Consecutive patients with acute ICH were prospectively enrolled. They were categorized into lobar or deep ICH. Lobar ICH were further divided in two subgroups according to CAA Boston criteria: probable CAA and other lobar ICH. Cortical florbetapir standard uptake value ratios (SUVr) were calculated using the whole cerebellum as a reference. Patients with lobar versus deep ICH, then patients with probable CAA versus other lobar ICH versus deep ICH, were compared for mean cortical florbetapir SUVr values.
Results: 39 patients (mean age = 65.5±11 years) with primary ICH were enrolled: 21 deep and 18 lobar ICH (10 with probable CAA). Mean cortical florbetapir SUVr was significantly higher among patients with lobar ICH than among patients with deep ICH (1.22±0.12 vs. 1.13±0.08; p=0.006). Patients with probable CAA had a higher cortical florbetapir SUVr than patients with other lobar ICH (1.28±0.08 vs. 1.13±0.11; p=0.008) or deep ICH (1.28±0.08 vs. 1.13±0.08; p<0.001). No difference was found between patients with other lobar ICH and deep ICH.
Conclusion: Cortical florbetapir uptake is increased among patients with lobar ICH, especially those with probable CAA. Florbetapir PET appears to be a promising tool for diagnosing CAA-related ICH.
Disclosure: This study was funded by Avid Radiopharmaceuticals, Toulouse Teaching Hospital (CHU) and the Institut des Sciences et du Cerveau de Toulouse.

P3103

Correlation between nitric oxide and cholinesterase levels in blood serum of patients with acute ischemic stroke

K. Rasulova
Tashkent, Uzbekistan

Background and aims: This study investigated the relationship between serum markers of endothelial dysfunction (the levels of NO metabolites) and cholinergic system (acetylcholinesterase activity) in atherothrombotic, lacunar, and cardioembolic strokes.

Methods: 100 ischemic stroke (IS) patients were recruited and divided into three groups: 42 with atherothrombotic stroke, 41 with lacunar stroke, 17 with cardioembolic stroke. In blood serum we determined NO2 and NO3 levels using Griss reactant, acetylcholinesterase (ACE) level by spectrophotometer method. Control group consisted of 20 patients without stroke.

Results: In IS the levels of NO metabolites significantly decreased on 37.3%. The most significant decrease of NO level was noted in cardioembolic stroke (on 40.4%). Serum level of acetylcholinesterase decreased on 24% that is evidence of cholinergic system deficit in IS, the most significant decrease was revealed in cardioembolic stroke (on 31.5%). Correlation analysis showed that NO level was straightly proportionally dependent on acetylcholinesterase level. This may indicate decreased stimulation of endothelial relaxation factor (NO) in stroke. We could find straight correlative interrelation of deficits of these substances in stroke subtypes, which was stronger in cardioembolic (r=0.79) and lacunar (r=0.72) and weaker in atherothrombotic stroke (r=0.68).

Conclusion: Endothelial dysfunction, characterized by endothelial NO reduction, and cholinergic neuromediation deficit, conditioned by decrease in cholinesterase level in blood serum of patients with IS, are considered to play the important role in the development of IS. NO reduction was found to be significantly correlated with serum level of cholinesterase and severity of ischemic stroke, especially in cardioembolic and lacunar strokes.

Disclosure: Nothing to disclose

P3104

Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorrain, France

S. Richard[1], L. Humbertjean[1], R. Fay[1], L. Durin[2], G. Mione[1], A.M. Enea[1], X. Ducrocq[1]
[1]CHU Nancy, Neurology, Nancy, France, [2]Agence de la Biomédecine, Direction Prélèvement Greffe organes - tissus, SRA Nord-Est, Nancy, France

Background and aims: Severe strokes are now the leading cause of brain death (BD). Potential donors require intensive care unit (ICU) management to protect organs while waiting for possible progression to BD. There are no established predictive factors to identify patients with a high probability of presenting BD.

Methods: We retrospectively collected clinical and paraclinical data of consecutive severe stroke patients with a potential progression to BD through the hospital organ procurement and transplant coordination system in five centers in Lorrain (France) between 1st January 2012 to 31st December 2013. Final endpoint was adjudicated BD. Statistical comparison of each factor was made between patients with and without BD. A prognostic score was made based on factors significantly associated with BD.

Results: Of 400 included patients 91 (23%) presented adjudicated BD. Initial Glasgow score ≤6 (p<0.0001), stroke volume >65 mL (p=0.040), herniation (p=0.038), hydrocephalus (p<0.0001), initial systolic blood pressure >150 mmHg (p=0.034) and past history of alcohol abuse (p=0.002) were significantly associated with BD progression (figure 1). In patients with quantifiable stoke volume the likelihood of presenting BD was 28 times greater for a score of 4 to 6 vs. 0 to 1 (p<0.0001) (table 1) (figure 2).

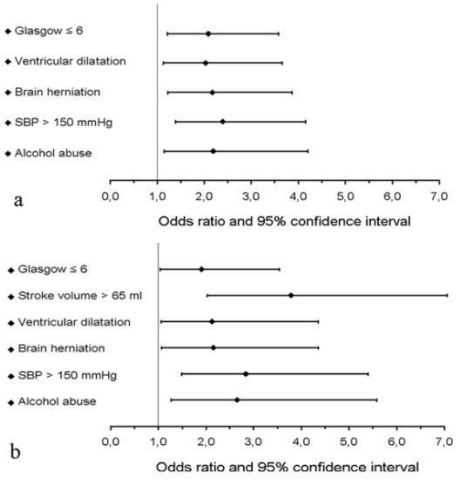


Figure 1: Factors significantly associated in multivariate analysis with brain death evolution for model 1 (a) and 2 (b). Model 1: model for stroke with non quantifiable volume, model 2: model for stroke with quantifiable volume

	Risk factors present	Units	OR (95% CI)	p
Model 1				
	0-1 factor		Ref	
	2 factors	vs. 0-1 factor	1.98 (0.89-4.44)	0.096
	3-5 factors	vs. 0-1 factor	7.91 (3.92-15.99)	<0.0001
Model 2				
	0-1 factor		Ref	
	2-3 factors	vs. 0-1 factor	5.66 (1.65-19.41)	0.006
	4-6 factors	vs. 0-1 factor	27.92 (8.24-94.58)	<0.0001

Table 1: Risk of brain death evolution according to model and number of predictive factors. Model 1: model for stroke with non quantifiable volume, model 2: model for stroke with quantifiable volume,

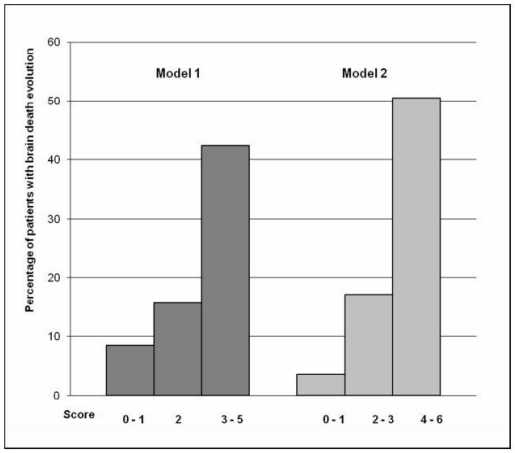


Figure 2: Percentage of patients with brain death evolution according to predictive score for model 1 and 2. Model 1: model for stroke with non quantifiable volume, model 2: model for stroke with quantifiable volume.

Conclusion: This is the first study to determine predictive factors for BD progression in severe stroke patients. It could be the basis of a simple tool of 6 criteria to help neurologists make the difficult decision of ICU management to preserve organs in potential organ donors.
Disclosure: Nothing to disclose

P3105
Abstract cancelled

P3106
Predictors of early neurological deterioration in acute ischemic stroke

A.F. Santos[1], J. Mota[2], L. Oliveira[3], L.M. Afonso[4], C. Machado[1], J.N. Alves[1], J. Pinho[1], C. Ferreira[1]
[1]Hospital de Braga, Neurology, Braga, Portugal, [2]Hospital de Santa Maria Maior - Barcelos, Internal Medicine, Barcelos, Portugal, [3]Centro Hospitalar do Médio Ave - Famalicão, Internal Medicine, Famalicão, Portugal, [4]Unidade Local de Saúde de Matosinhos, Internal Medicine, Matosinhos, Portugal

Background: Mild stroke symptoms are cited as the reason for not using rtPA in 29-43% of time-eligible patients. It is unknown whether the reversal of this decision, during hospital stay, changes the outcome.
Objective: Determination of early neurological deterioration predictors in acute ischemic stroke and outcome at 3 months.
Methods: Case control study. From a registry of rtPA treated patients (February 2007–September 2014) were identified 30 with NIHSS≤ 4 at admission and neurological worsening within the time window, subsequently submitted to thrombolysis. Risk factors, OCSP, TOAST and mRS at 3 months were noted. Control patients were 29, admitted during 2013, with NIHSS≤4, without worsening in the first day. Statistical analysis used SPSS Statistics 22.0.
Results: Mean age 67; 53% men. 20 had high blood pressure, 6 diabetics. 7 were on antiplatelets. One third PACI. Median NIHSS at the beginning of the infusion 9 (IQR = 7-10). ASPECT score 10 in 25; 4 had hyperdense middle cerebral artery (MCA). Mean time onset-to-needle: 198 minutes (SD = 75.8). Cardioembolic etiology in 30%. Patients with neurological deterioration had higher glycemia at admission than the control group ($p<0.05$). No other predictors of deterioration, including age, gender, OCSP, TOAST, ASPECTS, hyperdense MCA. Outcome was similar in both groups.
Conclusion: While waiting for scientific evidence to perform thrombolysis in patients with minor stroke, it is essential to maintain surveillance, particularly until 4,5 hours, namely in those with high glycemia. This treatment reversed the deleterious effect of neurological worsening in the acute phase.
Disclosure: Nothing to disclose

P3107

Influence of left ventricular dysfunction and related echocardiographic findings in ischemic stroke outcome

B.E. Sanz Cuesta[1], B. Fuentes Gimeno[1], P. Martínez Sánchez[1], M.T. López Fernández[2], J.J. Arévalo Manso[1], J. Díaz De Terán[1], I. Illán Gala[1], J. Rodríguez Pardo De Donlenbún[1], E.M. Alba Suarez[1], C. Calle De Miguel[1], J. Pérez Lucas[1], J. Máñez Miró[1], E. Miñano Guillamón[1], E. Díez Tejedor[1]
[1]Hospital Universitario La Paz, Neurology, Madrid, Spain, [2]Hospital Universitario La Paz, Cardiology, Madrid, Spain

Background and aims: Severe left ventricular systolic dysfunction (LVSD) is associated with increased morbidity and mortality in stroke. However, it is unknown whether left ventricular dysfunction (LVD) including mild to moderate LVSD and left ventricular diastolic dysfunction (LVDD) could influence ischemic stroke (IS) outcome. Increased left ventricular filling pressure (iLVFP) is a typical echocardiographic finding, which is present in both types of LVD of any severity, less known in IS. Our objective was to analyse LVD frequences and factors associated with unfavourable outcome including some LVD related echocardiographic findings.

Methods and Materials: Retrospective observational study in IS patients (Study period: 2010-2014). Demographics, vascular risk factors, results of diagnostic tests, reperfusion treatments and outcome at 3 months were collected (unfavourable if mRS≥3). The results of transthoracic echocardiography (TTE) including some of the most LVD related findings like left atrial enlargement >34 ml (LAE), left ventricular ejection fraction <35% (LVEF<35%) and iLVFP, were recorded. A predictive model of factors associated with unfavourable outcome was generated.

Results: 459 IS patients with TTE with LVD parameters measured. Mean age 67.8 years, 60.3% male. 70 (15.2%) had mRS≥3 at 3 months. 211 patients (46%) with LVD and 141 (30.7%) with iLVFP. 38 (8.3%) with LVSD and 191 (41.6%) with LVDD. iLVFP was associated with unfavourable outcome (OR 2.209, 95% CI 1.135- 4.299, p<0.020) after adjustment for diabetes mellitus, stroke severity and hospital complications.

Conclusion: Left ventricular dysfunction was present in almost half of the ischemic stroke patients. Increased left ventricular filling pressure was the only LVD related echocardiographic finding associated with poor outcome.

Disclosure: Nothing to disclose

P3108

The functional of the MnSOD Ala16Val, oxidative stress and markers of apoptosis as biomarkers in patients with stroke

A.E. Flores[1], E.T. Pascotini[1], A.L. Prado[1], A. Kegler[1], I.B. da Cruz[1], M.M. Duarte[1], R.S. Scalco[2], M.R. Fighera[3]
[1]Universidade Federal de Santa Maria, Santa Maria, Brazil, [2]University College London, London, United Kingdom, [3]Universidade Federal de Santa Maria, Neurology, Santa Maria, Brazil

Background and aims: The VV genotype associated with the Ala16Val polymorphism (MnSOD gene) has been associated with different health conditions including neurological disorders. Here we investigated the oxidative stress, apoptotic biomarkers and the Ala16Val polymorphism in patients with chronic stroke (CS).

Methods: A cross-sectional study of 40 CS patients and a control group of 40 healthy people was performed. Inclusion criteria included CS (>6 months after initial symptom). Clinical features were assessed by a standardized questionnaire and physical exam. Blood analysis included serum glucose (GLU), glycated hemoglobin (HBA1C), cholesterol (CHO), urea, phosphatase (PHO), acetylcholinesterase (AChE), low-density lipoprotein cholesterol (LDL), Protein Carbonyl (PC), caspase-1, caspase-3 and caspase-8. Statistical analyses were carried out using the SPSS statistical software, version 18.0 (SPSS Inc., Chicago, IL). Ala16Val genotype was presented in mean (%). T test was used to compare serum PC levels and serum caspase (1, 3 and 8) levels with clinical features (significance level was set at 5%).

Results: Patients with CS presented a higher frequency of the VV genotype (AA(32.5%), AV (27.5%) e VV(40%)) comparing to the control group ((AA 55% AV35% e VV 10%)). The serum PC (t=7.5 nmol/mg proteins), caspase-1(t=6.9 U/mg protein), caspase-3 (t=6.8 U/mg protein) and caspase-8 (t=6.7 U/mg protein) levels were increased in patients with CS compared to the control group. Other features of the CS group included GLU t=3.9mg/dL, HBA1C t=2.8%, CHO t=5.0mg/dL, LDL t=4.1mg/dL.

Conclusion: Our data suggest that the VV genotype may influence the oxidative stress response resulting in increased apoptotic markers in patients with CS.

Disclosure: Nothing to disclose

P3109

Combination of statin and inosine pranobex decreases the total rate of serum infectious pathogens immunoglobulins M and the incidence of post-stroke infections

E. Sidorovich[1], T. Amvrosieva[2], S. Likchachev[3], Z. Bogush[4], Y. Shabalina[5], I. Petrovich[5], B. Piskun[5]

[1]"National Research and Clinical Center Of Neurology and Neurosurgery, neurological, Minsk, Belarus, [2] The Republican Research and Practical Center for Epidemiology and Microbiology, Laboratory infections with natural reservoir, Minsk, Belarus, [3]National Research and Clinical Center Of Neurology and Neurosurgery, neurological, Minsk, Belarus, [4]The Republican Research and Practical Center for Epidemiology and Microbiology, Laboratory infections with natural reservoir, Minsk, Belarus, [5]Minsk city emergency hospital, neurological, Minsk, Belarus

Background and aims: Post-stroke infections being the result of the stroke-induced immunodepression worsen the ischemic stroke (IS) prognosis.

Methods: 148 patients with IS were randomly divided into 3 groups. The first group patients (n=54) received routine treatment including antiplatelet and symptomatic therapy. Excepting this treatment the second group patients (n = 45) received simvastatin 40mg/d or atorvastatin 20 mg/d. Adding to this therapy the third group patients (n = 49) received inosine pranobex (IP) 1000 mg thrise daily. Cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus, Helicobacter pylori, Mycoplasma pneumoniae, Chlamydia pneumoniae serum immunoglobulins (Ig) M were determined in IS patients using an enzyme-linked immunosorbent assay.

Results: The rates of infectious pathogens IgM in three IS groups were 27/54, 14/45 and 25/49 at the stroke onset. After 14 days of treatment the decrease in the rate of infectious pathogens serum IgM in the third group (22/25 - 84.0%) was higher than in the first (3/27-11.1%, $P<0.0001$) and in the second (4/14 – 28.6%, $P<0.001$) ones. In the third group the elimination of HSV and CMV IgM was noted in the majority of cases (17 from 22). The number of cases with poststroke infections in the third group (2.04%) was significantly lower than in the first (35.2%) and in the second (15.5%) groups of IS patients, $P<0.05$.

Conclusion: The results of the pilot study suggest that the combination of statin and IP having immunomodulatory as well as direct antiviral effect may prevent reactivation of latent infections and reduce the incidence of post-stroke infections.

Disclosure: Nothing to disclose

Child and developmental neurology 2

P3110

FMRI correlates of sustained attention in pediatric multiple sclerosis

E. De Meo[1], M.A. Rocca[1], L. Moiola[2], A. Ghezzi[3], P. Veggiotti[4], R. Capra[5], M.P. Amato[6], A. Fiorino[2], L. Pippolo[3], M.C. Pera[4], G. Comi[2], A. Falini[7], M. Filippi[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]Ospedale di Gallarate, Centro Studi Sclerosi Multipla, Gallarate, Italy, [4]C. Mondino National Neurological Institute, Department of Child Neurology and Psychiatry, Pavia, Italy, [5]Spedali Civili of Brescia, Regional Referring Center for Multiple Sclerosis, Brescia, Italy, [6]University of Florence, Department of NEUROFARBA, Florence, Italy, [7]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To assess fMRI abnormalities during a sustained attention task in pediatric multiple sclerosis (MS) patients and their correlations with cognitive dysfunction.

Methods: fMRI scans were acquired in 58 pediatric MS patients and 14 matched healthy controls (HCs) during the Conners' Continuous Performance Test (CPT). Patients with > 2 abnormal tests at neuropsychological evaluation were classified as cognitively impaired (CI).

Results: 20 patients were CI. With increasing task demand, all participants showed activations of bilateral parietal regions, middle frontal gyrus, supplementary motor area (SMA), right lingual gyrus and precuneus. Compared to HC, MS patients had an increased activation of left insula, anterior cingulate cortex and right inferior frontal gyrus, and a reduced activation of right precuneus and paracentral lobule. Compared to HC and CI, CP MS patients showed increased activation of left thalamus, inferior temporal and lingual gyri. Compared to the other two groups, CI MS patients had increased recruitment of the bilateral superior medial frontal gyrus, left SMA and right inferior frontal gyrus and cerebellum. They also experienced a reduced activation of the right postcentral gyrus (PCG). Better performance during CPT correlated with increased activity if the right precuneus and PCG, while worse CPT performance correlated with increased activity in frontal regions.

Conclusion: During and attentive task, CI and CP pediatric MS patients recruited different brain area with increasing task demand. The increased fMRI activity in frontal regions seen in CI MS patients is likely to be a maladaptive mechanism, associated with cognitive impairment.

Disclosure: Partially supported by a grant from Italian Ministry of Health (GR-2009-1529671).

P3111

Hand-foot-mouth disease neurologic complications: clinical features and parameters

T.-H. Eom
Seoul, Korea, Republic of

Background and aims: Hand-foot-mouth disease (HFMD) is a common childhood illness. Enterovirus 71 (EV71) epidemics have recently been associated with HFMD-based neurologic complications in the Asia-Pacific region. This study described HFMD clinical features, and investigated clinical parameters in patients presenting with acute neurologic complications associated with HFMD.

Methods: We retrospectively reviewed medical records from 235 hospitalized patients who developed HFMD with or without neurologic complications (22 and 213 cases, respectively) in Uijengbu, Korea between 2010 and 2013. Clinical manifestations, radiologic findings, cerebrospinal fluid analyses, virological analyses, and treatment regimens were summarized. Additionally, routinely collected baseline data from 235 patients were retrospectively analyzed to identify clinical parameters associated with neurologic complications.

Results: Brainstem encephalitis was the most frequent neurologic complication (11 cases), followed by aseptic meningitis (seven cases). We also found acute disseminated encephalomyelitis and meningitis retention syndrome. Both have rarely been reported in EV71-associated HFMD. Virological analyses were performed for 15 cases, and 14 demonstrated EV71 infection, while one patient demonstrated Coxsackievirus B3 infection. Multivariate logistic regression analysis indicated patients were more likely to develop neurologic complications if they experienced nausea/vomiting (OR=13.65, P<0.001) and lethargy (OR=10.68, P=0.003). Males were more likely to develop neurologic complications compared to females (OR=2.12, P=0.005). In addition, neurologic complications were associated with a higher peak heart rate (OR=1.13, P=0.001).

Conclusion: This study revealed usual and unusual findings of HFMD-associated neurologic complications. Male gender, nausea/vomiting, lethargy, and peak heart rate predicted HFMD-associated neurologic complications. However, laboratory findings did not reliably predict HFMD-associated neurologic complications.

Disclosure: Nothing to disclose

P3112

Abstract cancelled

P3113

Cognitive outcomes of children with fetal antiepileptic drug exposure at the age of 3-6 years – preliminary data.

N. Gogatishvili[1], T. Ediberidze[1], S. Mamukadze[1], G. Lomidze[2], N. Tatishvili[3], S. Kasradze[2]
[1]Tbilisi, Georgia, [2]Institute of Neurology and Neurophsychology, neurology, Tbilisi, Georgia, [32]Department of Neuroscience. M.Iashvili Children Central Hospital. Tbilisi. Georgia, Tbilisi, Georgia

Background and aims: Data on effects of intra-uterine exposure to antiepileptic drugs (AEDs) on cognitive functioning are limited and conflicting. Our aim was to assess the effects of fetal AEDs on cognitive outcomes in children.

Methods: In this retrospective cohort study children aged 3-6 years with fetal exposure to AEDs registered in the Georgian National AED-Pregnancy Registry of the European Registry of Antiepileptic Drugs (EURAP) were included. Neuropsychological assessments were performed in all using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI – IV), and Wide Range Assessment of Visual Motor Abilities (WRAVMA) tests. Statistical analysis was done using SPSS version 20 (SPSS Inc, Chicago, Illinois)

Results: So far 23 children were evaluated. 12 (52%) were exposed to valporate (VPA), 5 (22%) to carbamazepine (CBZ), 1 (4%) to lamotrigine (LTG), 3 (13%) to Phenobarbital (PB) and 2 (9%) to polytherapy with carbamazepine and levetiracetam (LEV). IQ scores were average (91-110) in 8 cases (35%), low (81-90) in 7 (30%), borderline (71-80) in 4 (17%) and extremely low (<71) in 4 (17%) children. 6 of 8 children with borderline and extremely low IQ were exposed to VPA mono-therapy. The 2 remaining were exposed to CBZ and PB, respectively.

Conclusion: These preliminary results indicate that 2/3 of children exposed to AEDs had reduced cognitive abilities, and most of them had been exposed to VPA monotherapy. More data are needed to establish significant conclusions.

Disclosure: The study was performed within the scientific grant-project " FR/373/8-313/13" from the Shota Rustaveli National Scientific Foundation.

P3114

Abstract cancelled

P3115

Diffusion tensor imaging of the auditory neural pathway for clinical outcome of cochlear implantation (CI) of pediatric congenital sensorineural hearing loss patients

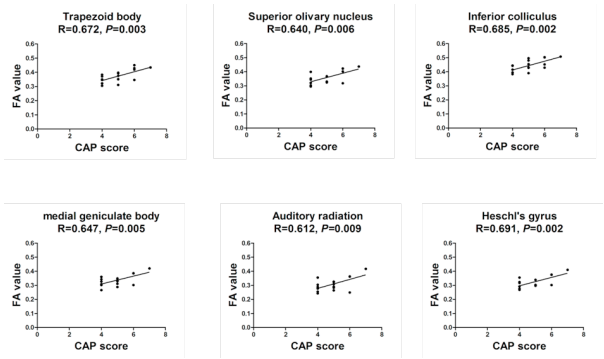
L. Huang[1], W. Zheng[1], C. Wu[2], X. Wu[3]
[1]The Second Affiliated Hospital, Medical College of Shantou University, Radiology, Shantou, China, [2]The Second Affiliated Hospital, Medical College of Shantou University, Radiology, Shantou, China, [3]The Second Affiliated Hospital, Medical College of Shantou University, E.N.T, Shantou, China

Background and aims: To evaluate possible changes in microstructure in auditory neural pathway of children with profound congenital sensorineural hearing loss (SNHL) and the possible difference between good and poor clinical outcome of cochlear implantation (CI) patients by using diffusion tensor imaging (DTI).

Methods: 30 patients (mean age, 4.6 years) with SNHL and 20 age-matched healthy controls underwent conventional MR imaging and DTI examination. Fractional anisotropy (FA) of six regions of interest (ROIs) positioned along the auditory pathwaythe trapezoid body (TB), the superior olivary nucleus (SON), the inferior colliculus (IC), the medial geniculate body (MGB), the auditory radiation (AR) and the white matter of Heschl's gyrus (WHG) were measured bilaterally in all subjects. Among the 30 patients, 17 patients with categories of auditory performance (CAP) score over 6 were classified into the good outcome group and 13 patients with CAP score below 6 were classified into the poor outcome group.

Results: FA values were significantly reduced at the six ROIs positioned along the auditory neural pathway of patients with SNHL compared with healthy controls, compared to good outcome subjects, poor outcome subjects displayed decreased FA values at all of the ROIs investigated in this study. Correlation analyses revealed strong correlations between FA values at all of the ROIs and CAP scores determined 12 months after CI.

Conclusion: Preoperative DTI imaging can be used to evaluate microstructural alterations in the auditory neural pathway that are not detectable by conventional MR imaging, and may play an important role in the evaluation of the outcome of the surgery.



Correlations between FA values and CAP scores at the selected brain regions(ROI); The lines are the result of a linear regression.

Disclosure: This study was supported by the Natural Science Foundation of Guangdong Province, China (2014), and was sponsored by Shantou University Medical College Clinical Research Enhancement Initiative(2014), Shantou China, Science and Technology Planning Project of Shantou City, China (grant No.201424260), Shantou China.

Clinical neurophysiology 2

P3116

Visual evoked potentials and retinal optical coherence tomography in optic neuropathy

N. El Ayoubi[1], H. Sawaya[2], R. Sawaya[1]
[1]Beirut, Lebanon, [2]American University Medical Center, Beirut, Lebanon

Background and aims: Flash (fVEP) and pattern reversal visual evoked potentials (PRVEP) study the physiological changes in the retinal neurons and axons, while retinal fiber layer (RNFL) and ganglion cell/internal plexiform layer (GCIPL) seen on optical coherence tomography (OCT) reflect the size of the respective layers. The aim of this study is to correlate these different variables in normal eyes and patients with chronic optic neuropathy (ON).

Methods: We studied 14 normal eyes and 13 eyes with optic neuropathy. All eyes were stimulated with intermittent light and pattern reversal stimulation, monocularly with high-contrast checkerboard pattern, at a reversal rate of 2 Hz, with a check size of 30', and an average of 150 stimulations. OCT was performed using Spectral-Domain Cirrus® OCT Device. RNFL and GCIPL were measured. Multiple statistical methods were used.

Results: The mean and standard deviation of fVEP, PRVEP, RNFL, GCIPL was calculated for controls and patients with ON (table 1). We found a negative correlation between PRVEP and RNFL in the control group (fig 1), and a negative correlation between fVEP and GCIPL in the ON eyes (fig 2).

	Mean (SD)	
	Controls	ON
fVEP (ms)	155.86 (24.33)	130.77 (44.62)
prVEP (ms)	104.64 (3.54)	145.15 (35.09)
OCT RNFL (µm)	98.57 (7.1)	83.18 (20.27)
OCT GCIPL (µm)	89.43 (3.74)	71.27 (10.61)

Fig.1: Mean and SD of fVEP, PRVEP, RNFL and GCIPL in normal and ON eyes.

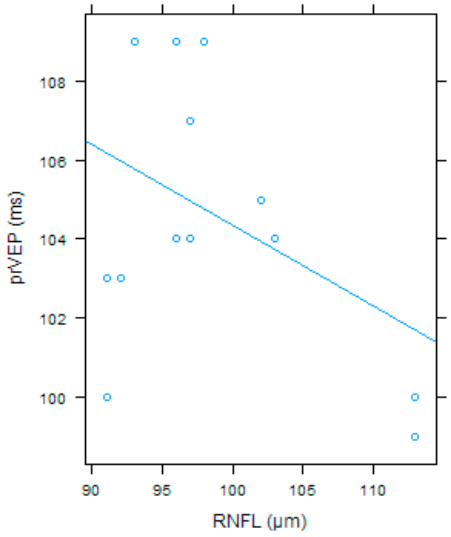


Fig.2: PRVEP latencies and RNFL in controls.

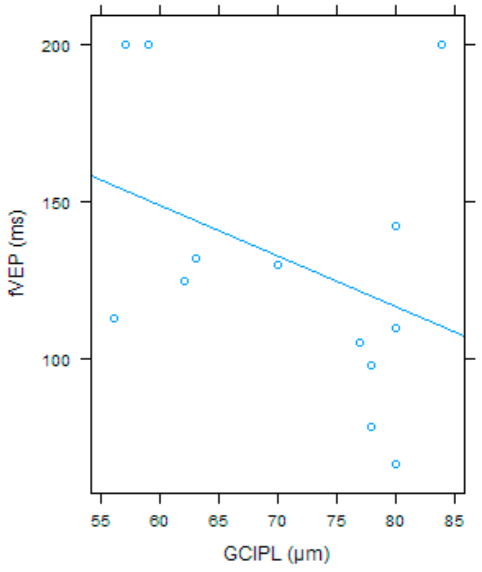


Fig.3: fVEP latenices and GCIPL in ON eyes.

Conclusion: In controls PRVEP is shorter and less variable than fVEP. It correlates with RFNL size, but does not reflect changes in the GCIPL. In ON PRVEP is delayed while fVEP is shorter and more variable than in controls. Furthermore, in ON fVEP reflects GCIPL thickness more than PRVEP.

Disclosure: Nothing to disclose

P3117

The VEMP score: a promising marker of disability progression in patients with multiple sclerosis

T. Gabelic[1], M. Krbot Skoric[1], I. Adamec[1], M. Habek[2]
[1]Zagreb, Croatia, [2]University Hospital Center Zagreb, Neurology, Zagreb, Croatia

Background and aims: Vestibular evoked myogenic potentials (VEMP) have been recognized as a reliable method in detection of symptomatic and asymptomatic brainstem involvement in multiple sclerosis (MS). Recently developed VEMP score showed significant correlation with EDSS and disease duration in MS patients in a cross-sectional study.

The aim of this study was to evaluate the VEMP score as a marker of disability progression in MS patients.

Methods: 26 patients with definitive diagnosis of relapsing-remitting MS underwent clinical, neuroradiological and neurophysiological work up at the study entry consisting of expanded disability status scale (EDSS), brainstem functional system (BSFS), presence of brainstem lesions on the brain MRI and ocular and cervical VEMPs. For these 26 patients second complete clinical and neuroradiological analysis with additional data about number of relapses, number of total new T2 lesions and new gadolinium enhancing lesions was done after three years and results were correlated with the VEMP score value at the study entry.

Results: EDSS at follow-up was significantly correlated with values of the VEMP score at the study entry ($p=0.048$; $R=0.392$). Significance with the VEMP score was also observed for follow-up values of BSFS ($p=0.050$; $R=0.389$). No statistically significant correlation was found between VEMP score and number of gadolinium enhancing lesions or number of clinical relapses.

Conclusion: The VEMP score shows promise as a marker of future disability development in patients with relapsing-remitting MS.

Disclosure: Nothing to disclose

P3118

Optical coherence tomography and multifocal visual evoked potentials can be useful in clinical practice when full-field visual evoked potentials fail in identifying visual pathway abnormalities.

S. Guerrieri[1], G. Di Maggio[1], F. Vitali[2], R. Santangelo[1], S. Medaglini[1], L. Moiola[1], U. Del Carro[1], V. Martinelli[1], G. Comi[1], L. Leocani[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [2]San Raffaele Scientific Institute, Department of Neurophysiology, Milan, Italy

Background and aims: Full-field visual evoked potentials (ff-VEP) are fundamental in neurological practice, for detecting and defining the nature of visual disturbances or to identify subclinical involvement of the visual pathway. We explored whether, in case of normal ff-VEP and suspected organic visual pathway involvement, multifocal visual evoked potentials (mf-VEP) and optical coherence tomography (OCT) can be useful in the diagnostic workup.

Methods: Observational case reports.

Results: We described the cases of three patients arrived at our Neurology department for visual disturbances. Two patients had relapsing optic neuritis (ON) and visual acuity (VA) loss, with normal or not significant ff-VEP outside acute clinical episodes. In both cases OCT scan showed a reduction of global retinal nerve fiber layer (RNFL) thickness, allowing visual pathway damage identification. Another patient with left frontal basal meningioma involving the left optic nerve arrived at our department complaining of blurred vision in the nasal visual field of the left eye as confirmed by computerized perimetry (CP). While ff-VEP showed a normal latency and a non significant amplitude reduction in the left eye, mf-VEP showed an important amplitude reduction in the whole lower left eye visual field. OCT scan confirmed axonal damage showing left global and sectoral RNFL thinning.

Conclusion: Sometimes ff-VEP fails in identifying abnormalities in patients with organic pathological processes involving the visual pathway, particularly in cases with axonal or sectoral optic nerve involvement. We suggest the importance of a multimodal instrumental evaluation, including OCT and mf-VEP.

Disclosure: Part of this work was supported by Merck Serono S.A., Geneva, Switzerland. Merck Serono is the biopharmaceutical division of Merck KGaA, Darmstadt, Germany.

P3119

Pattern reversal visual evoked potentials variability with age

R. Sawaya[1], S. Hammoud[1], H. Sawaya[2], W. Radwan[1]
[1]Beirut, Lebanon, [2]American University Medical Center, Beirut, Lebanon

Background and aims: Pattern reversal visual evoked potential (PRVEP) is an electrophysiological test to study the optic nerves and tracts. This study aims at evaluating the changes in the latencies and amplitudes of the PRVEP across the different age groups in normal subjects to standardize this technique, produce average results for the different decades, and to evaluate the changes across age groups.

Methods: We studied 81 healthy participants (162 total eyes), between the ages of 20 and 92 divided into decades. Stimulation was performed monocularly with high-contrast (>50%) black-white checkerboard pattern, at a reversal rate of 2 Hz, with a check size of 30', a band-pass of 1-100 Hz, a sweep of 250 msec, and an average of 150 stimulations. Multiple statistical methods were used.

Results: We define the mean and standard deviations for the latencies and amplitude for each decade (table 1). Trend analyses showed that there was a significant linear trend by age for all three latencies, indicating that the higher age groups had longer latencies We found that the latencies dip at the 4th decade before increasing in the older age groups (fig 1). The amplitude of N75-P100 decreases with age (fig 2).

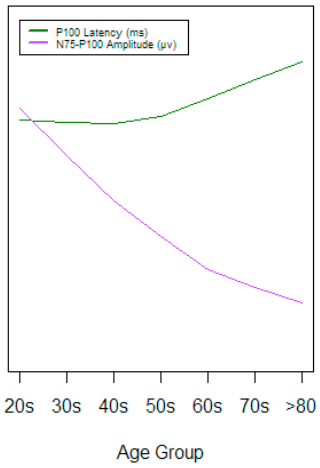


Fig. 1: Latencies vs amplitude a cross age categories.

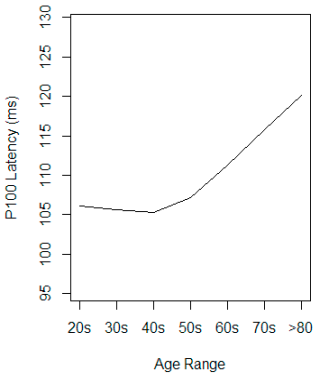


Fig. 2: P100 latencies across age categories.

	N75	P100	N145	Amplitude
Age Groups	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
20s	74.93 (3.96)	105.75 (3.57)	146.96 (12.13)	11.26 (5.79)
30s	77.4 (4.64)	107.54 (3.56)	149.04 (9.98)	8.35 (3.86)
40s	72.67 (3.46)	103.25 (4.5)	136.41 (9.66)	7.57 (3.67)
50s	74.06 (5.39)	105.73 (6.67)	143.5 (12.87)	6.72 (3.18)
60s	77.25 (9.73)	112.4 (6.23)	149.15 (9.78)	5.64 (2.38)
70s	78.9 (7.09)	115.1 (5.53)	150.05 (14.57)	5.51 (2.41)
≥ 80	83.61 (9.74)	118.05 (7.79)	153.95 (11.23)	5.9 (3.52)

Table1: Means and standard deviations of prVEP N75, P100 and N145 Latencies (ms) and N75 – P100 Amplitude (µv) for the different age groups

Conclusion: We define the N75, P100 and N145 latencies across the different age groups and conclude that the latencies increase with age while the N75-P100 amplitude decreases. Latencies are shortest in the 4th decade.

Disclosure: Nothing to disclose

P3120

Age-related changes in neurophysiology according to gender

I. Gomes[1], A.C. Siviero[2], L.E. Hauck[3], R. Siciliani Scalco[4], J. Becker[5]
[1]PUCRS, Neurology, Porto Alegre, Brazil, [2]ULBRA, Porto Alegre, Brazil, [3]Plau, Germany, [4]Porto Alegre, Brazil, [5]PUCRS and ULBRA, Neurology, Porto Alegre, Brazil

Background and aims: Age and gender related physiological changes are common and are to be expected. It is however not clearly standardized how these factors can affect normal neurophysiological reference limits and frequently a common average reference is generally used to report neurophysiological studies of the peripheral nervous system in both male and female patients

Methods: We retrospectively analysed 4,622 upper limb and 3,896 lower limb neurophysiological reports with results within the normal limits to identify age-related changes according to gender.

Results: Both sensory and motor conduction studies showed age-related amplitude and conduction velocity decreases and distal latency increases (motor conduction studies). These findings were even seen in younger age groups and progressively changed over life in different ways according to gender.

Conclusion: Understanding the expected normal range of neurophysiological results according to age group and gender may have an important practical application as it may improve diagnostic criteria of normality.

Disclosure: Nothing to disclose

P3121

Mystery beneath the abductor pollicis brevis atrophy: a case series

B. Bastan[1], P. Kahraman Koytak[2], H. Alibas[2], K. Uluç[2]
[1]Haseki Educational and Research Hospital, Neurology, Istanbul, Turkey, [2]Marmara Univercity Faculy of Medicine, Neurology, Istanbul, Turkey

Background and aims: Atrophy of the abductor pollicis brevis (APB) muscle is a well-known presentation of severe carpal tunnel syndrome (CTS) and motor neuron disorders (MND). However, it may be seen in other disorders. The purpose of this case series is to document the different etiologies causing thenar atrophy other than CTS and MND.

Methods: We prospectively evaluated 15 patients presenting to our clinic with atrophy of the abductor pollicis brevis muscle, without clinical and electrophysiological evidence of CTS and/or MND between January and December 2013. All of the patients underwent electrophysiological investigation, magnetic resonance imaging (MRI) of the cervical spine and MRI of the hand muscles, when necessary.

Results: 7 patients had electrophysiological and radiological evidence of cervical radiculopathy, with 6 of them showing isolated involvement of C8-T1 roots. One patient had C8-T1 root avulsion. 3 of the cases had brachial plexopathy, in which 2 of them revealed typical features of neurogenic thoracic outlet syndrome. 1 patient had syringomyelia and another patient had proximal median neuropathy. 2 of the patients were found to have agenesis of APB muscle which was confirmed by hand MRI. Needle electromyography of these patients showed no acute denervation potentials or motor unit potentials in the APB muscle whereas needle examination of the other median innervated muscles and other C8-T1 root innervated muscles was normal.

Conclusion: Cervical radiculopathy is the most common cause of thenar atrophy in patients without signs of CTS and/or MND. Although it is a very rare condition, agenesis of APB muscle should be included the differential diagnosis.

Disclosure: Nothing to disclose

P3122

Two cases of lipoatrophy after local steroid injection

I. Kim, S. Lee
Korea, Republic of

Background and aims: Local corticosteroid injections are frequently included as treatment option in clinical guidelines in the field of musculoskeletal disorders. Adverse effects of systemic steroid medication are well known to the public, whereas the side effects of local steroid injections, were not known to even clinicians and there is a potential threat to misdiagnosis. We report two cases of localized lipoatrophy and depigmentation following local steroid injection.

Case Reports: A 43-year-old woman was referred to our clinic with a 4-month history of depressed skin and numbness in back of the hand. She underwent a local triamcinolone injection around the right first metacarpal joint to alleviate the pain of radial collateral ligament injury 4 months ago. Examination revealed atrophy of the skin, hypopigmentation, and hypoesthesia in the right first dorsal interosseous area (Figure 1) without weakness. An 18-year-old female visited our clinic with a 3-month history of depression in her left medial foot. Four months ago, she had been treated for a presumed plantar fasciitis with local steroid injection. Examination revealed a prominent tissue atrophy and depigmentation between navicular prominence and instep (Figure 2). Electrodiagnostic studies of the two cases showed no abnormalities

Figure 1

Figure 2

Conclusion: Although the incidence of soft tissue atrophy after local steroid injection is reported less than 1%, it will increase in proportion to the frequency of the procedure. Many practitioners classify these adverse effects as 'trivial' and leave out of consideration. However, even clinicians, who do not perform the injection, should be aware of the occurrence of this cosmetically disturbing side effect.

Disclosure: Nothing to disclose

P3123

A 5-year follow-up of visual evoked potentials and nerve conduction study in adolescents with type 1 diabetes mellitus

S. Lee[1], H. Kim[2], H.-S. Han[3]
[1], Korea, Republic of, [2]Chungbuk National University School of Medicine, Preventive Medicine, Cheongju-si, Korea, Republic of, [3]Chungbuk National University School of Medicine, Paediatrics, Cheongju-si, Korea, Republic of

Background and aims: Central nervous system impairment is common in diabetic patients, even in the early stages of the disease, and could be associated with peripheral neuropathy. The aim of the study was to prospectively investigate central nerve conduction changes in adolescent with type 1 diabetes using pattern-reversal visual evoked potentials (PRVEP) and to determine how those results were related to clinical risk factors and parameters of peripheral nerve conduction studies (NCS).

Methods: A total of 36 type 1 diabetic patients (15 males), 5-24 years of age (mean 14.5±4.7), underwent PRVEP and NCS annually for five years. For comparison, 39 healthy adolescents (mean 14.8±5.0) were studied.

Results: The P100 latencies of PRVEP were prolonged at the study entry when compared with controls ($P<0.001$). Significant correlations were not found between the parameters of PRVEP and HbA1C levels, but on the other hand the parameters of peripheral NCS were well correlated to the metabolic control. The latency and amplitude values of P100 were not related to any parameter of NCS.

Conclusion: Prolonged PRVEP latency may be a sign of optic pathway dysfunction which begins before the apparent diabetic retinopathy. Poor glycemic control proved to be an important risk factor as related to the development of peripheral neural pathway abnormalities. However, central conduction changes were poorly related with diabetic control and attributes of peripheral nerve conduction studies over the 5 year follow-up. There was no significant change in the parameters of PRVEP in adolescents with type 1 diabetes mellitus during the relatively early stage of the disease.

Disclosure: Nothing to disclose

Cognitive neurology/ neuropsychology 2

P3124

Predictors of Quality of Life in patients with multiple sclerosis

I. Moreira[1], R. Samoes[1], E. Santos[1], C. Pinto[2], A. Gonçalves[2], S. Cavaco[2], A. Martins Silva[1]
[1]Centro Hospitalar do Porto - Hospital Santo António, Neurology, Porto, Portugal, [2]Centro Hospitalar do Porto - Hospital de Santo António, Neuropsychology Unit, Porto, Portugal

Background and aims: Quality of life (QoL) is commonly affected in patients with Multiple Sclerosis (MS) and is considered an important outcome measure in clinical trials. Our aim was to explore associations between patients' demographic, clinical, psychopathological and cognitive features and indicators of QoL in MS.

Methods: In a population of 419 patients with MS, 270 patients (62% women; age=39±11; education=12±5 years; EDSS=3±2; disease duration=10±9 years; 85% relapsing-remitting course, 8% secondary progressive, 7% primarily progressive) answered the Functional Assessment of Multiple Sclerosis Scale (FAMS) and the Hospital Anxiety and Depression Scale (cut off > 11 for anxiety and depression), and underwent a neuropsychological assessment (cognitive impairment was defined as >25% neuropsychological measures <5th percentile). Mann-Whitney test, Pearson's r, and multiple linear regressions (without variable selection) were used for statistical analysis.

Results: Negative associations ($p<0.05$) were found between QoL scores (FAMS) and female gender, increasing age, longer disease duration, higher EDSS, progressive course of disease, anxiety, depression, and cognitive impairment. QoL increased with education ($p<0.05$). Multiple linear regression analysis showed that EDSS (β adjusted = -5.375), anxiety (β adjusted = -17.781), depression (β adjusted = -31.789), and cognitive impairment (β adjusted = -7.861) remained statistically associated with FAMS total score when controlling for demographic characteristics sex, age and education.

Conclusion: Neurological disability, psychopathological symptoms, and cognitive functioning were robust predictors of QoL in this population with MS. The study results are consistent with the literature and underscore the importance of addressing mood and cognition in the clinical management of MS patients.

Disclosure: Nothing to disclose

P3125

Cognitive evolution inTysabri treated multiple sclerosis patients

F. Jacques[1], B. Harel[2], A. Schembri[3], C. Paquette[1], B. Bilodeau[1], P. Kalinowski[3]
[1]Clinique Neuro-Outaouais, Gatineau, Canada, [2]Cogstate, New Haven, USA, [3]Cogstate, Melbourne, Australia

Background and aims: Cognitive dysfunction affects up to 65% of MS patients and progresses over time.
The objectives of this study are to understand the impact of natalizumab on cognition beyond two years of therapy and to investigate whether baseline characteristics are predictive of clinical response.

Methods: This is a single-center, 24-month, observational study. 63 patients treated with natalizumab were assessed prior to monthly infusions using a Cogstate battery and the SDMT. A linear mixed model was conducted with duration of natalizumab therapy as a between-subjects factor (≤2 or >2 years), assessment as a within-subjects factor, and MSSS as a covariate. All patients in the ≤2 years group were treated with natalizumab for less than two years prior to baseline. All patients in the >2 years group were treated with natalizumab for at least two years prior to the baseline (mean 3.6 years).

Results: There were no statistically significant differences between the key demographic variables aside for the MSSS ($p=.0074$). No patient showed evidence of sustained cognitive deterioration over the 24 month period. Irrespective of time on natalizumab, significant improvements were observed at the group level in executive function, verbal memory and working memory, whereas processing speed and attention remained unchanged. Impaired cognition or any other baseline parameter did not influence the trajectory of cognitive change over 24 months.

Conclusion: Our results suggest that natalizumab preserves cognitive function, including the ability to learn, for 4 years and beyond of continuous therapy. This occurs irrespective of baseline characteristics.

Disclosure: The research has been financed by an unrestricted grant from Biogen Idec.

P3126

Brain on Track: development of a self-administered web-based test for longitudinal cognitive assessment

L. Ruano[1], A. Sousa[2], M. Severo[1], I. Alves[2], M. Colunas[3], R. Barreto[2], C. Mateus[2], S. Moreira[2], E. Conde[3], V. Bento[4], N. Lunet[1], J. Pais[2], V. Tedim Cruz[2]

[1]University of Porto Medical School, Department of Clinical Epidemiology, Predictive Medicine and Public Health, Porto, Portugal, [2]Entre Douro e Vouga Hospital Center, Neurology, Santa Maria Da Feira, Portugal, [3]University of Aveiro, Clinical Research Office, Health Sciences Department, , Aveiro, Portugal, [4]University Institute of Maia – ISMAI, Maia, Portugal

Background and aims: Follow-up testing has been recommended to improve the diagnostic reliability of cognitive screening and patient monitoring strategies. However, few brief asessement tools have been validated for this purpose. Our objective is to develop a web-based self-administered test intended for repeatable cognitive assessment (Brain on Track).

Methods: A team of neuropsychologists and neurologists designed several computerized subtests, expected to evaluate different cognitive domains. An initial (Test A) and a refined subtest battery (Test B) were applied to patients with mild cognitive impairment or early stage dementia (n=88) and matched controls (Study I). Principal component and internal consistency analysis were performed. The area under the Receiver Operating Characteristic (ROC) curve and the Smallest Real Difference (SDR) were estimated. A subsample of a population-based cohort (n=113) performed Test B from home every 3 months (Study II). Test-retest reliability was evaluated using two-way mixed single intraclass consistency correlation coefficient (ICC).

Results: Cronbach's alpha was 0.91 for Test A and 0.90 for Test B. For both tests A and B, the total scores were significantly different between patients and controls ($p = 0.001$), with the SDR (3.74 and 4.18) being lower than the clinical relevant difference (4.00 and 4.82). The area under ROC curve was 0.66 and 0.73. In a 3 trial analysis of test-retest reliability, 9/10 subtests showed high ICC (≥ 0.74).

Conclusion: The Brain on Track test showed good internal consistency, discriminative ability and reliability when performed from home. Undergoing clinical and population-based prospective studies will allow for further refinement and validation for longitudinal clinical use.

Disclosure: Nothing to disclose

P3127

Hemiprosopometamorphopsia as the presenting symptom of Marchiafava-Bignami disease

M. Tábuas-Pereira, J. Parra, D. Duro, A.M.C. Maduro, M.I.J. Santana

Coimbra, Portugal

Background and aims: Cognitive deficits that compromise the perception and recognition of faces are related to fusiform area, especially the right fusiform gyrus, which is central in prosopagnosia. Hemiprosopometamorphopsia is a rare deficit in perception of face configuration, related mainly with ischemic lesions (located in the retrosplenic or unilateral temporoocipital regions). Marchiafava-Bignami is a rare toxic disease seen mostly in chronic alcoholics that results in progressive demyelination and necrosis of the corpus callosum.

Case Report: A 59-year-old right-handed man, presented with changes in the perception of the right half of the human faces, which seemed deformed and somehow longer. These changes have been progressively developing for some days/weeks. He did not show neither signs of alexia/dyslexia, colour anomia, optic aphasia, apraxia, agraphia nor other cognitive or neurological deficits. The changes were restricted to the faces. MRI showed a lesion in the left side of the splenium of the corpus callosum. OCT and Hess-Lancaster found no changes. Blood and CSF analysis showed only a reduction of folic acid levels. The patient reported subjective feeling of improvement with vitamin supplementation. MRI performed six months later showed central necrosis of the lesion, with no enlargement.

Conclusion: Hemiprosopometamorphopsia is a rare symptom (less than 15 cases reported) but with a high localization value. It is associated with disconnection of the occipital lobe with the contralateral fusiform area. Being bizarre, it may be overlooked as of psychiatric nature. Here, we present the first report of hemiprosopometamorphopsia as a presenting sign of a patient with Marchiafava-Bignami syndrome.

Disclosure: Nothing to disclose

P3128

Hippocampal-DMN disconnectivity in MS is related to WM lesions and contributes to depression

L. Vacchi[1], M.A. Rocca[1], E. Pravatà[2], P. Valsasina[1], M. Radaelli[3], B. Colombo[3], C. Gobbi[4], G. Comi[3], A. Falini[5], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]Neurocenter of Southern Switzerland, Department of Neuroradiology , Lugano, Switzerland, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]Neurocenter of Southern Switzerland, Department of Neurology, Lugano, Switzerland, [5]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: The hippocampus is part of the default-mode network (DMN) and is functionally hit early in the course of multiple sclerosis (MS). We hypothesized that white matter focal lesions may contribute, through a disconnection mechanism, to hippocampal dysfunction and hippocampal-related clinical deficits. To test this, we assessed the relationship between abnormalities of hippocampal resting state (RS) functional connectivity (FC) with brain T2 lesion volumes and presence and severity of depression.

Methods: Structural and RS fMRI images were acquired from 69 cognitively intact MS patients and 42 matched healthy controls (HC). In patients, depression was quantified using the Montgomery-Asberg Depression Rating Scale. Hippocampal RS FC was assessed using a seed-voxel approach. SPM8 was used for between-group comparisons and analysis of correlation between RS FC abnormalities with clinical and structural MRI variables.

Results: Compared to HC, MS patients experienced a significant atrophy of the whole brain and left hippocampus ($p<0.001$) as well as a distributed pattern of decreased RS FC between the hippocampi and several cortical-subcortical regions. Reduced hippocampal RS FC with the DMN was strongly correlated to higher T2 lesion volume as well as to disease duration, severity of depression and disability.

Conclusion: In cognitively preserved MS patients, brain focal WM lesions influence the functional integration of the hippocampus to other brain regions of the DMN, leading to a disconnection syndrome. Such a disruption of hippocampal RS FC contributes to the occurrence of depression and to clinical disability.

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P3129

Does fast titration of topiramate reveal the early detection of patients who will experience negative cognitive side effects?

G. Widman, J.A. Witt, C.E. Elger, C. Helmstaedter

Universität Bonn, Klinik für Epileptologie, Bonn, Germany

Background and aims: Topiramate (TPM) is effective for migraine-prophylaxis, treatment of epilepsy, obesity, neuropathic pain, and alcohol-dependence. Executive dysfunction, however, is a common adverse side effect, which may significantly affect daily functioning. Additionally, anosognosia for these changes has been suggested, when they develop slowly under normal titration.

For treatment of refractory status epilepticus, however, a titration up to 400mg within one day was reported without severe non-cognitive side effects.

Methods: Executive functions before and after fast (n=10 with 50mg /day) versus slow titration (n=15 as recommended) were compared using the screening tool EpiTrack®. End doses were comparable with 215mg/day and 220mg/day respectively

Results: With fast titration, objective deficits in executive functions increased from 50% at baseline to 80% at follow-up, and 70% experienced a significant decline. With slow titration deficits increased from 53% to 73% with significant declines in 47% of the patients.

Conclusion: Faster titration of TPM may help to avoid disastrous numbness after dismissal, but 23% more patients than with low titration experience decline in executive functions. A controlled study with longer follow up will be necessary in order to evaluate whether patients with fast titration habituate and have outcomes as observed with slow titration.

Disclosure: Nothing to disclose

P3130

Spatial attention and the feeling of bodily self in the elderly

D. Zeller, M. Hullin
Univ. of Würzburg, Dept. of Neurology, Würzburg, Germany

Background and aims: In young adults, a right-hemispheric specificity has been suggested for spatial attention and for the feeling of body-ownership. Here, we aimed at assessing these neuropsychological functions, which may be modulated by age, in the elderly.

Methods: 65 subjects with median age of 75 (60-90) years without a neurological history were included. Spatial attention was assessed by the Milner landmark task, which requires a judgment of asymmetry of centrally pre-bisected lines. The spontaneous feeling of limb ownership was inquired by a questionnaire. To experimentally manipulate this feeling, we used the "rubber hand illusion" (RHI) paradigm. Synchronous or asynchronous brushstrokes were applied to the subjects' hidden real hand and an aligned plastic hand. The occurrence of the illusion was assessed by subjective (questionnaire) and objective (proprioceptive drift) measures.

Results: Spatial attention was asymmetric, with 63±26% ($p<0.001$) overestimation of the right segment of the mid-bisected line. In all subjects except for one, the spontaneous feeling of limb-ownership was unimpaired. Subjective responses indicated an experience of the RHI during synchronous, but not asynchronous stimulation, without lateralization. The proprioceptive drift towards the plastic hand following synchronous stroking was comparable between sides (1.4±2.0/1.7±2.7cm, right/left). At the left hand, however, the proprioceptive drift correlated significantly with the rightward bias of spatial attention.

Conclusion: In the healthy elderly, neither subjective nor objective RHI measures were lateralized on group level. However, asymmetric spatial attention may influence the multisensory process of „embodiment" of an artificial hand, as indicated by correlation. Further studies will assess body-related multisensory integration in neurological conditions.

Disclosure: Nothing to disclose

P3131

AD8 informant screening questionnaire for cognitive impairment: pragmatic diagnostic test accuracy study

B. Ziso[1], B. Stagg[2], M. Rawle[1], A. Larner[1]
[1]Walton Centre Neurology and Neurosurgery, Neurology, Liverpool, United Kingdom, [2]Alzheimer's Society, Liverpool, United Kingdom

Background and aims: To report the diagnostic accuracy of AD8, a brief informant screening questionnaire for the detection of dementia and cognitive impairment.

Methods: Prospective observational study, Cognitive Function Clinic.

Results: Of 334 consecutive patients seen between July 2013 and July 2014, 212 (M:F = 106:106; age range 16-92 years, median 64.5 years) attended with a suitable informant. No informant declined when invited to perform AD8. Of the 212 patients, 69 were diagnosed with dementia (DSM-IV-TR criteria), 62 had MCI (Petersen criteria). Using the cut off ≥2/8 ("cognitive impairment is likely to be present"; higher AD8 scores are worse) as defined in the index paper (Galvin et al. 2005), AD8 score was sensitive (0.97) but not specific (0.17) for cognitive impairment. Looking at all AD8 scores, the most accurate cut off (0.67) was ≥2/8. Area under the ROC curve was 0.67. AD8 scores showed no correlation with patient age ($r=0.019$) and low correlations with cognitive screening instrument scores (MMSE and 6CIT: $r = -0.23$ and 0.37, respectively).

Conclusion: AD8 is simple to administer and score. In this pragmatic diagnostic test accuracy study AD8 was sensitive but not specific for identifying patients with cognitive impairment.

Disclosure: Nothing to disclose

Epilepsy 2

P3132

Neuroprotective effects of allopregnanolone in a pilocarpine-induced status epilepticus mouse model

W.-J. Kim, I. Cho, H.-J. Kim, H.-W. Kim
Yonsei University, College of Medicine, Neurology, Seoul, Korea, Republic of

Background and aims: Oxidative stress released by seizure is related to the epileptogenesis. The SOD is responsible for destroying free radicals, thereby keeping normal condition between ROS and antioxidant defense system. Some of neurosteroids are known to show wide anticonvulsant effects and alter neuronal excitability through interaction with GABAA receptor. We investigated the role of ROS in prolonged seizure-induced neuronal death and the possible mechanism of neuronal protection underlying allopregnanolone, one of neurosteroids, thereby detecting SOD expression in pilocarpine-induced status epilepticus mouse model.

Methods: Adult male C57BL/6 mice were given injections of pilocarpine 30 min after scopolamine treatment. In allopregnanolone group, we treated with several dosages of allopregnanolone after SE. Hippocampal cell death was assessed by cresyl violet and TUNEL staining. The ROS was assessed using in situ detection of oxidized hydroethidine (HEt) administered intravenously after SE. SOD level was analyzed by both western blotting analysis and immunofluorescent staining in hippocampus.

Results: A decrease in the number of neuronal cells was clearly observed and TUNEL positive cells were significantly increased in hippocampal CA1 and CA3 regions, except for the region of DG, 3 days after SE. In allopregnanolone group, the ROS of production, TUNEL positive cells, and oxidative DNA damage were significantly decreased compared to vehicle-injected group. SOD expression, meanwhile, was increased in hippocampus both Western blot and immunestaining analysis in allopregnanolone-treated group.

Conclusion: Excessive ROS clearly induces neuronal death through neuronal DNA damage in a hippocampus, and allopregnanolone has a neuroprotective effect in response to oxidative stress by altering the SOD level in brain.

Disclosure: Nothing to disclose

P3133

Congruency of MR imaging and histopathologic diagnosis in surgically treated patients with epilepsy

M. Kovacevic[1], S. Raicevic[2], D. Damjanovic[3], I. Nikolic[3], V. Bascarevic[4], A. Ristic[1], N. Vojvodic[1], S. Jankovic[1], J. Milin Lazovic[5], D. Sokic[1]
[1]Clinical Center of Serbia, Center for Epilepsy and Sleep Disorders, Neurology Clinic, Belgrade, Serbia, [2]Clinical Center of Serbia, Pathohistology Department, Belgrade, Serbia, [3]Clinical Center of Serbia, Radiology and Magnetic Resonance Imaging Center, Belgrade, Serbia, [4]Clinical Center of Serbia, Institute for Neurosurgery, Belgrade, Serbia, [5]Medical School, University of Belgrade, Institute for Medical Statistics and Informatics, Belgrade, Serbia

Background and aims: Underlying pathology of focal epilepsy is an important predictor of seizure outcome after surgery. While histopathologic (HP) findings are the gold-standard, brain magnetic resonance imaging (MRI) is an important tool in preoperative assessment of underlying pathology. The aim of our study was to evaluate the congruency of MRI diagnosis of epileptogenic lesions with histopathologic findings in surgically treated patients with focal epilepsy.

Patients and methods: We identified 88 surgically treated patients with lesional focal epilepsy evaluated at the Neurology Clinic, Clinical Center of Serbia. 10 patients were eliminated due to insufficient data. 3 patients had normal HP findings. The remaining 75 patients (33 male, 34.6±9.9 years) were classified according to HP as hippocampal sclerosis (HS), 2) malformations of cortical development (MCD), 3) tumors, 4) vascular malformations (VM) and 5) other pathologies. MRI of operated patients were post hoc analyzed by two radiologist blinded to surgical and PH outcome and compared to PH diagnosis.

Results: Congruency existed in 39/41 (95.1%) patients with HS (three with undetected FCD type IIIa); 4/12 (33.3%) with MCD; 11/14 (68.8%) with tumors (two with undetected FCD type IIIb); 4/4 (100.0%) with VM and 2/4 (50.0%) with other pathologies. Overall, MRI correctly identified the diagnosis in 60/75 (80.0%) patients.

Conclusion: In most patients with lesional focal epilepsy, MRI can correctly identify the underlying pathology, especially in patients with HS, VM and tumors. A provisional MRI diagnosis is important for presurgical planning and may have prognostic implications.

Disclosure: Nothing to disclose

P3134

Pro-inflammatory cytokines in patients with mesial temporal lobe epilepsy with and without co-morbid depression

O. Kukhlenko

Danylo Halytsky Lviv National Medical University, Department of Neurology and Neurosurgery , Lviv, Ukraine

Background and aims: Depression is a frequent psychiatric disorder in patients with temporal lobe epilepsy (TLE). Nowadays it is established that major endogenous depression is associated with inflammation. However, genesis or maintenance of depression in patients TLE has to be better understood. The aim of our study was to evaluate the state of pro-inflammatory cytokines profile in blood plasma of patients with mesial temporal lobe epilepsy with and without co-morbid depression.

Methods: Concentrations of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17) and C-reactive protein (CRP) were evaluated in blood plasma by the ELISA method. Hamilton depression rating scale and DSM-IV criteria were used for the diagnosis of co-morbid depression. We examined 26 patients with mesial TLE and hippocampal sclerosis signs on MRI. All the patients took carbamazepine as antiepileptic monotherapy and had similar rate of seizures frequency.

Results: Received data revealed increase in plasma IL-6 concentration in patients with TLE and major depression 21.4±1.4pg/ml while compared with MTLE patients without major depression – 12.5±1.1pg/ml ($p<0.05$). Concentration of IL-1β in patients with co-morbid depression was higher, but did not differ reliably ($p>0.05$). There was reliably higher mean concentration of IL-17 in patients with major depression – 12.6±1.2pg/ml, while in non-depressed patients – 8.6±1.0pg/ml ($p<0.05$). No reliable differences between both studied groups in concentration of C-reactive protein were found.

Conclusion: There is an evidence that hyperproduction of pro-inflammatory cytokines IL-6, IL-17 may be involved in the pathogenesis of major depression in TLE.

Disclosure: Nothing to disclose

P3135

ABCB1/MDR1 gene polymorphisms and the level of apoptotic factors in epilepsy patients treated with antiepileptic drugs

U. Lagan-Jedrzejczyk[1], A. Oczkowska[2], A. Florczak[3], J. Florczak-Wyspianska[1], J. Karczewski[4], A. Swiejkowska[4], K. Wiktorowicz[4], E. Przedpelska-Ober[1], W. Kozubski[1], J. Dorszewska[5]

[1]Chair and Department of Neurology, Poznan, Poland, [2]2Laboratory of Neurobiology, Department of Neurology, Poznan, Poland, [3]Laboratory of Neurobiology, Department of Neurology, Poznan, Poland, [4]Department of Biology and Environmental Studies, Poznan, Poland, [5]Laboratory of Neurobiology, Department of Neurology,Poznan University of Medical Sciences, Poznan, Poland

Background and aims: The antiepileptic drug (AED) therapy besides its clinical side effects may also induce plenty of molecular changes including the level of apoptotic factors. The ABCB1/MDR1 gene may modulate the pathways of suicidal cell death.

The aim of the study was to analyze the frequency of C3435T and C1236T polymorphisms of ABCB1/MDR1 gene, homocysteine (Hcy) and methionine (Met) concentration, the level of apoptotic proteins (p53, Bax, Bcl-2) and apoptotic cells in epilepsy patients, before and during AEDs treatment and in controls.

Methods: The study involved 57 epilepsy patients (18 – 69 aged) and 24 controls (22 – 61 aged). Genetic study was conducted using PCR-RFLP, plasma biothiols concentration was analyzed by HPLC/EC, the levels of apoptotic proteins in peripheral lymphocytes by Western blotting method and the level of lymphocyte apoptotic cells by active caspase-3 detection by flow cytometry.

Results: The study has shown that AEDs therapy in epilepsy patients leads to changes in plasma biothiols concentration and the level of apoptotic factors. The frequency of CC genotype of ABCB1/MDR1 C1236T and beneficial for treatment TT C3435T of this gene was higher in epilepsy patients than in control group. Epilepsy patients with genotype TT C3435T in combination with CC C1236T well responded to older AEDs in monotherapy and with CT C1236T to newer anticonvulsants.

Conclusion: It seems that in epilepsy patients treated with AEDs only ABCB1/MDR1 C3435T polymorphism is connected with regulation of the apoptotic cells level.

Genetic analysis of ABCB1 gene polymorphisms in epilepsy patients may lead to the more successful therapy.

Disclosure: Nothing to disclose

P3136

Effectiveness of eslicarbazepine acetate as add-on treatment to antiepileptic monotherapy in adults with partial-onset seizures (EPOS study): analysis by baseline antiepileptic drug

C. Lawthom[1], R. McMurray[2], R. Sousa[3], M. Holtkamp[4]
[1]Royal Gwent Hospital, Newport, Wales, United Kingdom, [2]Eisai Europe Ltd, Hatfield, United Kingdom, [3]Bial -Portela & Cª, S.A., S. Mamede do Coronado, Portugal, [4]Charité - Universitätsmedizin Berlin, Berlin, Germany

Background and aims: Eslicarbazepine acetate (ESL) is approved as a once-daily adjunctive therapy for adults with partial-onset seizures (POS), with or without secondary generalisation. The prospective, non-interventional Eslicarbazepine acetate in Partial-Onset Seizures (EPOS) study investigated the effectiveness and safety/tolerability of ESL as add-on to antiepileptic monotherapy in everyday clinical practice across eight European countries. Here we present an analysis of ESL's effectiveness by baseline antiepileptic drug.

Methods: Adult patients with uncontrolled POS under antiepileptic monotherapy, whose clinician had previously and independently decided to initiate ESL add-on therapy, were included if they provided informed consent. Retention rate at 6 months (primary endpoint), time to ESL discontinuation and responder rate (response defined as ≥50% seizure frequency reduction from baseline) were assessed according to the most frequent baseline monotherapies (>10% of patients).

Results: Of 219 patients included in the study, 83, 54 and 30 received baseline monotherapy with levetiracetam (LEV), lamotrigine (LTG) and valproate (VAL), respectively. Retention rates (95% confidence intervals) at 6 months were 85.5% (76.1–92.3%) for LEV, 75.9% (62.4–86.5%) for LTG and 80.0% (61.4–92.3%) for VAL. Mean times to ESL discontinuation were 96.9 days (LEV), 90.8 days (LTG) and 88.8 days (VAL). Responder rates at 6 months ranged from 69.8% (LTG) to 88.5% (VAL) (Table 1).

Table 1. Responder rate at 3 and 6 months by baseline monotherapy

Visit	All (N=219)		LEV (N=83)		LTG (N=54)		VAL (N=30)	
	Valid N	n (%)	Valid N	n (%)	Valid N	n (%)	Valid N	n (%)
Month 3	209	146 (69.9)	76	53 (69.7)	54	36 (66.7)	29	23 (79.3)
Month 6	187	153 (81.8)	72	59 (81.9)	43	30 (69.8)	26	23 (88.5)

Conclusion: ESL as add-on to antiepileptic monotherapy was effective independently of the type of monotherapy to which it was added. These findings must be interpreted with caution due to low subgroup patient numbers.

Disclosure: Study Supported by Eisai.

P3137

Genetic variation in GRIN2B and clinical characteristics of mesial temporal lobe epilepsy with hippocampal sclerosis

B. Leal[1], J.M.M. Chaves[1], D. Boleixa[2], C. Carvalho[3], A. Bettencourt[3], J. Freitas[1], J.M.C.F. Lopes[1], J.E.D.P. Ramalheira[1], R. Rangel[4], P. Pinho Costa[5], A. Martins da Silva[6], B. Martins da Silva[7]
[1]Porto, Portugal, [2]Abel Salazar Institute of Biomedical Sciences, University of Porto – ICBAS/UP, Unit for Multidisciplinary Research in Biomedicine (UMIB), Porto, Portugal, [3]Autoimmu and NeuroScien, Unidade Multidisciplinar Invest Biomed, Inst Ciencias Biomed Abel Salazar, UPorto, Porto, Portugal, [4]hospital santo antónio - centro hospitalar do porto, Porto, Portugal, [5]Instituto nacional de saúde Dr. Ricardo Jorge, Porto, Portugal, [6]Hospital Santo António - Centro Hospitalar do Porto, Porto, Portugal, [7]Autoimmu and NeuroScien, Unidade Multidisciplinar Invest Biomed, Inst Ciencias Biomed Abel Salaza, Porto, Portugal

Background and aims: Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS) is the most frequent pharmaco-resistant epilepsy. Some authors claim that up to 80% of MTLE-HS patients have antecedents of complex FS and the existence of a genetic basis that underlie both conditions has been postulated. Several studies have demonstrated that glutamate receptor NMDA, particularly its subunit NR2B, has lower gene expression in brain tissue from epileptic patients. Function and expression of this subunit may be influenced by several polymorphisms in GRIN2B gene. Our aim was to analyse the association between rs7301328 and MTLE-HS development and clinical characteristics in a Portuguese population.d.

Methods: A cohort of 163 MTLE-HS patients (91F, 72M, mean age= 44.1±11.7 years, age of onset= 13.5±10.6 years, 82 with febrile seizures antecedents) was compared with a cohort of 272 healthy individuals (HI) in a case-control genetic association study. rs7301328 was genotyped by Taqman PCR methodology.

Results: Genotypic and allelic frequencies were similar between patients and controls., independently of FS antecedents.

Conclusion: Our results show that disease predisposition is not dependent of rs7301328, at least, in the population studied.

Disclosure: Nothing to disclose

P3138

Abstract cancelled

P3139

Efficacy of adjunctive perampanel in idiopathic generalised epilepsy: Subgroup analysis of patients with absence and myoclonic seizures in a double-blind placebo-controlled Phase 3 trial

T.J.O'Brien[1], B.J. Steinhoff[2], H. Yang[3], A. Laurenza[3], A. Patten[4], F. Bibbiani[3]

[1]Royal Melbourne Hospital, Melbourne, Australia, [2]Kork Epilepsy Centre, Kehl-Kork, Germany, [3]Eisai Neuroscience Product Creation Unit, Woodcliff Lake, NJ, USA, [4]Eisai Neuroscience Product Creation Unit, Hatfield, Hertfordshire, United Kingdom

Background and aims: Adjunctive perampanel was shown to be efficacious in reducing primary generalised tonic-clonic seizures (PGTCS) in patients with idiopathic generalised epilepsy (IGE) (French et al., AES 2014). We assess the effects of adjunctive perampanel on absence and myoclonic seizures in these patients.

Methods: Patients ≥12 years with ≥3 PGTCS in the 8 weeks before randomisation, receiving 1–3 concomitant anti-epileptic drugs for ≥30 days before baseline were eligible to enrol. The study had pre-randomisation (4-week screening, 4–8-week baseline) and randomisation (4-week titration, 13-week maintenance, 4-week follow-up) phases. Perampanel was increased weekly by 2 mg to 8 mg/day or individual optimal dose. Secondary endpoints included median percent change from baseline and 50% responder rate for absence and myoclonic seizures.

Results: The full analysis set comprised 162 patients (81 placebo; 81 perampanel). 37.0% of patients experienced absence seizures and 29.0% experienced myoclonic seizures during pre-randomisation. The study was not powered to detect differences in these seizure types, however, there was a numerical reduction in absence seizures with perampanel versus placebo. Myoclonic seizures were reduced in both treatment arms, but the decrease was greater in placebo patients (Table 1). Similar proportions of perampanel and placebo patients experienced an increase in myoclonic seizures (Table 2). Overall, perampanel did not worsen myoclonic seizures. Seizure freedom across all seizures for perampanel versus placebo was 23.5% versus 4.9%.

Conclusion: Adjunctive perampanel reduces PGTCS in patients with IGE. When assessing other generalised seizure types, compared with placebo, adjunctive perampanel improved absence seizures and did not aggravate myoclonic seizures.

Disclosure: Study funding: Eisai Inc. Medical writing support: Choice Healthcare Solutions, funded by Eisai Ltd.

Table 1. Efficacy of adjunctive perampanel in absence and myoclonic seizures

Seizure type, %	n				P-value
	PBO	PER	PBO	PER	
			Median baseline seizure frequency/28 days		
PGTC	81	81	2.50	2.55	
Absence	33	27	8.15	13.00	
Myoclonic	23	24	3.50	13.75	
			Median % change from baseline in seizure frequency[a]		
PGTC	81	81	−38.38%	−76.47%	P<0.0001
Absence	33	27	−7.58%	−41.18%	P=0.3478[c]
Myoclonic	23	24	−52.54%	−24.47%	P=0.6100[c]
			50% responder rate[b]		
PGTC	81	81	39.5%	64.2%	P=0.0019
Absence	33	27	39.4%	48.1%	P=0.4653[c]
Myoclonic	23	24	60.9%	41.7%	P=0.3694[c]

[a]Median percent change during titration and maintenance periods vs baseline.
[b]Responder: ≥50% reduction in seizure frequency per 28 days during the maintenance period vs baseline.
PBO, placebo; PER, perampanel; PGTC, primary generalised tonic-clonic.
[c]The study was not powered to detect differences in these seizure types.

Table 2. Increase in seizure frequency/28 days from pre-randomisation in myoclonic seizures

Percent change category	PBO (n=23) n (%)	PER (n=24) n (%)
+0–≤25	3 (13.0%)	2 (8.3%)
+>25–≤50	1 (4.3%)	1 (4.2%)
+>50–≤75	0	1 (4.2%)
+>75–<100	0	0
+100	3 (13.0%)	3 (12.5%)
Total	7 (30.4%)	7 (29.2%)

The study was not powered to detect differences in myoclonic seizures. PBO, placebo; PER, perampanel.

Movement disorders 7

P3140

Functional movement disorders: diagnostic and management patterns in a Portuguese cohort

R. Barreto, V.T. Cruz
CHEDV, Neurology, Feira, Portugal

Background and aims: Functional movement disorders (FMD) are frequent in specialized and non-specialized clinical practice and often entail significant loss of quality of life. Their heterogeneity and link to psychiatric problems complicate diagnosis and appropriate treatment. We aim to review all FMD cases and follow-up presented to our department until September 2014.

Methods: Review of hospital database for episodes compatible with DMF (according to Fahn-Williams criteria). Excluded other functional pathologies such as pseudoepileptic seizures.

Results: 36 patients were selected (67% female). Symptoms began between the age of 6 and 80 (mean = 52 years), the average duration of symptoms at first observation was 3.3 years. One-third of the cases did not present psychiatric backgrounds. The most frequent phenomenon was tremor (56%), followed by myoclonus (17%) and dystonia (8%). The average time of follow-up was 15 months, 28% of patients were still in follow-up, 81% initiated or maintained psychotropic drugs, 44% were referred to psychiatry and 8% to physical therapy. Half of the patients underwent one or more tests due to FMD: neuro-radiological (39%), neurophysiological (22%) and genetic testing (8 percent). Currently, after a mean period of 7 years (range: 1-30 years), 42% of patients still show symptoms of FMD.

Conclusion: In our study, FMD occurred in all age groups, being that most patients obtained a late diagnosis, which is known to carry a worse prognosis. The use of psychoactive drugs was more common than multidisciplinary referral. The high chronicity rate reflects the complexities of treatment in FMD. Future prospective population-based studies can be very important.

Disclosure: Nothing to disclose

P3141

Quantitative finger tapping assessment based on inertial sensors - assistance in differential diagnostics of parkinsonism

M. Djuric-Jovicic[1], M. Ječmenica-Lukić[2], I. Petrović[3], S. Radovanović[4], N. Dragasevic[2], V. Bobić[5], M. Belić[1], V.S. Kostic[2]
[1]University of Belgrade, School of Electrical Engineering, Innovation center, Belgrade, Serbia, [2]University of Belgrade, Medical faculty, Clinical centre of Serbia, Neurology Clinic, Belgrade, Serbia, [3]Belgrade, Serbia, [4]University of Belgrade, Institute for Medical Research, Belgrade, Serbia, [5]University of Belgrade, School of Electrical Engineering, Belgrade, Serbia

Background and aims: In clinical practice, the finger tapping movement is often validated visually, thus resulting in a coarse diagnostic resolution. However, using the appropriate instrumentation, finger tapping performance can be quantified, allowing objective assessment of specific characteristics or changes in the finger tapping pattern over time.

Methods: By using miniature inertial sensors, mounted on fingertips on index finger and thumb, various parameters such as cadence, tapping duration, opening and closing speed, tapping angle were extracted for detailed analysis of patients' motor performance. Besides listed kinematic parameters, acquired data were preprocessed using continuous wavelet transformation (CWT), and their coefficients were used in further analysis of spectral content. Based on cross-sections of CWT in time and frequency, we introduced parameters describing characteristic tapping frequencies and vigor of the performed movements. The study included 16 patients with Parkinson's disease (PD), 18 patients with progressive supranuclear palsy (PSP), 18 patients with multiple system atrophy (MSA), and 14 age and gender matched healthy subjects.

Results: In this way, characteristic frequency areas, high activity sequences, motor blocks and decrement in time can be identified and observed. These parameters were further used in classification for distinction between the four groups, achieving more than 85% classification accuracy among groups, offering support for differential diagnostics.

Conclusion: Using the proposed sensors and methodology, quantitative assessment of repetitive finger tapping performance can be obtained thus providing support in monitoring the patient's state, response to therapy as well as in differential diagnostics of parkinsonism.

Disclosure: The work on this study was supported by the Serbian Ministry of Education, Science and Technological Development under Grant No. 175090, and Grant No. 175016.

P3142

Phosphorylated α-synuclein biomarker in skin nerves is differently expressed in pure autonomic failure and idiopathic Parkinson's disease

V. Donadio[1], A. Incensi[1], C. Piccinini[1], P. Cortelli[2], M.P. Giannoccaro[1], A. Baruzzi[1], R. Liguori[1]
[1]IRCCS Istituto Scienze Neurologiche Bologna, UOC Clinica Neurologica, Bologna, Italy, [2]University of Bologna, Department of Biomedical and Neuromotor Sciences, Bologna, Italy

Background and aims: This study defines the expression in skin nerves of native and misfolded (phosphorylated) α-synucleins in pure autonomic failure (PAF) and idiopathic Parkinson disease (IPD), two synucleinopathies with different clinical phenotypes and pathogenesis. The specific aims were to: 1) define the importance of native (n-syn) and phosphorylated (p-syn) α-synucleins as disease biomarkers; 2) ascertain differences in abnormal skin nerve deposits that may justify a different pathogenesis.

Methods: We studied 30 patients including 16 well-characterized IPD patients and 14 patients fulfilling the diagnostic criteria for PAF. 30 age-matched healthy subjects served as controls. Subjects underwent skin biopsy from proximal (i.e. cervical) and distal (i.e. thigh and leg) sites to study small nerve fiber and intraneural n-syn and p-syn.

Results: PAF and IPD patients showed a length-dependent small fiber neuropathy, more severely expressed in patients with higher p-syn load. N-syn was similarly expressed in both groups of patients and controls. By contrast, p-syn was not found in any skin sample of controls but was found in all PAF and IPD patients. Nevertheless, abnormal p-syn deposits differed between IPD and PAF both in spatial distribution and pattern of innervation.

Conclusion: 1) p-syn was a reliable in vivo marker of IPD and PAF whereas n-syn should not be considered a disease marker; 2) neuritic p-syn inclusions differed in IPD and PAF suggesting a different underlying pathogenesis; but 3) they were associated with a length-dependent small fiber neuropathy in both disorders suggesting a similar effect on peripheral nerve fiber dysfunction.

Disclosure: Nothing to disclose

P3143

Botulinum toxin injections are effective to treat foot dystonia and pain associated in Parkinson's disease

F. Durif[1], I. Rieu[2], E. Durand[3], B. Pereira[4], M. Simonetta Moreau[5], F. Ory-Magne[5], S. Sangla[6], D. Guehl[7], S. Soulayrol[8], F. Fluchère[9], T. Rouaud[10], D. Gayraud[11], C. Geny[12], B. Degos[13], C. Vial[14], G. Castelnovo[15], P. Derost[3]
[1]Clérmont-Ferrand, France, [2]CHU , Clermont-Ferrand, France, [3]CHU Clermont-Ferrand, Neurology, Clermont-Ferrand, France, [4]CHU Clermont-Ferrand, Biostatistic Unit, Clermont-Ferrand, France, [5]TOULOUSE, France, [6]AP-HP, Paris, France, [7]Pessac, France, [8]Aubagne, France, [9]AP-HM, Marseilles, France, [10]Hopital Laënnec, Neurology, Nantes, France, [11]CH Aix en Provence, Aix en provence, France, [12]CHU Montpellier, neurology, Montpellier, France, [13]AP-HP, neurology, Paris, France, [14]Hospices Civils de Lyon, Service d'ENMG et pathologies neuromusculaires, Lyons, France, [15]CHU Nimes, Neurology, Nimes, France

Background and aims: Botulinum toxin (Btx) injections seem to be effective to treat foot dystonia. However studies on this topic are few and very imprecise. This double bind randomized study was undertaken to evaluate if intramuscular injections of Btx in Flexor Digitorum Longus (FDL) or Flexor Digitorum Brevis (FDB) are beneficial to reduce dystonia and associated pain in parkinsonian patients with foot dystonia (vs placebo injections) and determinate which site of injection is the most efficient.

Methods: 45 patients were randomized in 3 groups: "FDB"group (1 injection of placebo in FDL/1 injection of Btx (100U- Xeomin) in FDB), "FDL"group (1 injection of placebo in FDB/1 injection of Btx in FDL) and the "PL"group (1 injection of placebo in FDB and FDL). Patients were injected 2 times spaced in 3 months. Six weeks after each injection, clinical state improvement, duration and severity of dystonia, pain and quality of life were evaluated.

Results: The 3 groups were not significantly different in terms of age, disease duration, treatment and dystonia (duration/severity/pain). Patients treated by Btx groups (FDB+FDL) showed an improvement of the clinical state and a reduction of pain and dystonia ($p<0.05$ vs J0) with no difference in quality of life. Clinical state and pain improvement was significantly higher in Btx groups vs PL group ($p<0.05$). Considering the injection site, clinical state tended to be more improved in FDL group vs FDB group ($p=0.08$).

Conclusion: Btx injections are effective to treat foot dystonia and pain associated. Injection in FDL muscle tended to be more beneficial.

Disclosure: Financial support : MERZ society

P3144

Diagnostic value of 24h urinary copper excretion after 48h of d-penicillamine cessation in compliance assessment in Wilson's disease patients

K. Dziezyc[1], T. Litwin[2], G. Chabik[2], A. Członkowska[2]
[1]Warsaw, Poland, [2]Institute of Psychiatry and Neurology, 2nd Department of Neurology, Warsaw, Poland

Background and aims: Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism. Treatment with anti-copper agents is effective in most cases. However, compliance is essential. Urinary copper excretion is an important parameter for diagnosis and treatment monitoring. During long-term treatment with chelating agents, a two-day interruption in treatment should result in normal values of urinary copper concentration (<50μg/dl). The aim of this study was to establish the usefulness of this method in compliance assessments in these patients.

Methods: We examined consecutive patients treated with d-penicillamine (DPA) for a minimum of one year undergoing routine follow-up studies at our center. We assessed copper metabolism parameters, neurological examinations, hepatic status, and compliance. We performed 24-h urinary copper excretion analysis 48h after an interruption in chelating therapy.

Results: 33 patients were enrolled. The mean treatment duration was 11.78±11.75 years. After 48h of DPA cessation, normalization (<50μg/24h) in copper excretion was observed in 20 (87%) of 23 compliant patients. Ten patients were non-compliant and copper excretion was above 50μg/24h in 7 (70%) of them after cessation of DPA. The specificity and sensitivity of this test was 87% and 70%, respectively. Receiver operator curve analysis found an optimal cut-off of urinary copper excretion of 62μg/dl for compliant patients.

Conclusion: Measurement of 24-h urinary copper excretion after a 48-h interruption in DPA therapy in patients with WD is a reliable method for confirming patients' compliance and may be helpful for further treatment decisions.

Disclosure: Nothing to disclose

P3145

Frequencies of initial gait disturbances and falls in 100 Wilson's disease patients

K. Dziezyc[1], T. Litwin[2], G. Chabik[2], A. Członkowska[2]
[1]Warsaw, Poland, [2]Institute of Psychiatry and Neurology, 2nd Department of Neurology, Warsaw, Poland

Background and aims: Wilson's disease (WD) is an inherited disorder of copper metabolism. Gait disturbances may present with both extrapyramidal and cerebellar patterns. However, so far frequency of particular types of gait abnormalities were not established. Thus, the aim of our study was to establish the frequency of initial gait disturbances among our neurological WD patients.

Methods: We analyzed gait disturbances at the time of diagnosis in neurologic feature WD patients diagnosed between 2005 and 2014. Assessment was based on Unified Wilson's Disease Score Scale (UWDRS). In UWDRS, gait abnormalities are divided into three main patterns: dystonic, ataxic, parkinsonian. All type of gait impairment were assessed with four stages of severity (0-normal, 4-severe). History of falls also was obtained.

Results: 103 patients were diagnosed between 2005 and 2014. 3 patients with severe neurological impairment, unable to walk were excluded from analysis. Gait abnormalities were observed in 59% of patients. The most frequent (45%) was ataxic gait which manifests mainly as impaired tandem. Parkinsonian gait was noted in 18% (11/59), and dystonic gait in 10% (6/59) of patients. Mixed type of gait impairment was observed in 25% (15/59) of patients (ataxic, dystonic, and parkinsonian n=8, ataxic and parkinsonian n=7). Falls were noted in 35% patients, but in most cases were occasionally observed.

Conclusion: Gait disturbances in WD are frequent.The most common is ataxic gait and mixed disturbances. Complex gait abnormalities in WD reflect involvement of many brain structures.

Disclosure: Nothing to disclose

P3146

Does "Botox" make stupid? –The effect of botulinum toxin on cognition

K. Elwischger, M. Schmöger, U. Willinger, C. Abdel-Aziz, J. Alger, S. Pretscherer, E. Auff, T. Sycha, G. Kranz
Medical University of Vienna, Department of Neurology, Vienna, Austria

Background and aims: Recent work has indicated changes of emotional processing after cosmetic botulinum toxin (BoNT) therapy. Thereby, proprioceptice afferences from facial muscles have been proposed to boost emotional processing via facial feedback loops. In this study, we investigated the effect of BoNT on higher cognitive functions.

Methods: 84 subjects, 19 patients with cranial dystonia and hemifacial spasm, 32 patients with cervical dystonia and 33 matched healthy control subjects were recruited. All patients had been injected repeatedly before and were recruited from our BoNT outpatient clinic. At baseline, all subjects performed the „verbal analogies test" for verbal reasoning, and the subtest „matrices" of the Intelligence Structure Test 2000-R for non-verbal reasoning. All patients received their routine BoNT treatment after baseline testing. Three weeks after baseline, the tests were repeated.

Results: The intelligence scores revealed no differences at baseline between the three groups. Three weeks after baseline, patients with injections in facial muscles scored worse ($p=0.022$ in the non-verbal subtest; $p=0.051$ in the verbal test), whereas patients with cervical injections and controls remained unchanged. We found no correlation between BoNT-dose and intelligence scores.

Conclusion: Our data suggest a reversible negative short term-effect on non-verbal intelligence scores (and trend wise in verbal scores) when facial muscles are treated with BoNT. Similar to emotional processing, proprioceptive feedback loops from facial muscles might have a positive effect on concentration and cognition.

Disclosure: Nothing to disclose

P3147

Evaluation of gait and posture in essential tremor before and after unilateral Gamma knife thalamotomy

B. Emmanuelle[1], T. Witjas[1], R. Carron[2], J. Regis[2], J.-P. Azulay[1], M. Vaugoyeau[3], A. Eusebio[1]
[1]Marseilles, France, [2]CHU La Timone, Marseilles, France, [3]CNRS, Marseilles, France

Background and aims: Essential tremor (ET) is characterized by a progressive postural and kinetic tremor affecting the arms, responsible for a functional impairment in daily activities. Its pathophysiology remains poorly understood and therapeutic options are limited. Some clinical and experimental data suggest a cerebellar involvement. However, few data exist regarding gait and posture impairment in ET. The aim of our study was to describe specific features of gait disorders and postural instability in patients with severe ET, and to evaluate the effect on these motor skills of a unilateral Gamma Knife thalamotomy (GKT).

Methods: 19 patients with severe ET were included; we analysed gait and posture before and one year after unilateral GKT, using a multiparametric automatized movement analysis system.

Results: Our results show a significant decrease of step length, cadence and velocity in ET compared to age-matched controls. Patients with head and upper limb tremor had a higher impairment of gait than patients with isolated upper limb tremor. Posturo-locomotor skills were compared for each patient before and after radiosurgery, and statistical analyses reveal no effect of unilateral GKT on gait and posture.

Conclusion: This study confirms postural instability and gait impairment in ET, which may be related to a dysfunction of cerebello-thalamo-cortical pathway. Our results suggest that head tremor could be correlated with a more severe gait impairment. Specific involvement of cerebellum, or alteration of visuo-vestibular input caused by head movements, could deteriorate postural control. Our work shows no deleterious effect of unilateral GKT on posture and gait, requiring confirmation on larger population.

Disclosure: Nothing to disclose

P3148

Case series: post-operative edema associated with delayed delirium after DBS surgery in Parkinson's disease

C. Fricke[1], J.-J. Rumpf[1], T. Woost[1], D. Weise[2], D. Winkler[2], J. Meixensberger[2], J. Classen[1]

[1]Universitätsklinikum Leipzig, Neurology, Leipzig, Germany, [2]Universitätsklinikum Leipzig, Neurosurgery, Leipzig, Germany

Background and aims: Deep brain stimulation (DBS) has been used to treat advanced stages of Parkinson's disease (PD) in patients without major cognitive deficits. Some studies suggest that cognitive function may decline after DBS. We here investigated whether delayed post-operative delirium is associated with edema surrounding DBS leads.

Methods: We evaluated patients who were implanted with DBS for PD in 2013 and 2014 at the university hospital of Leipzig. Each subject received a cranial CT following surgery; the majority of patients additionally received an MRI several days later. We analyzed the frequency of postoperative edema and its association with documented deliria occurring during the postoperative period.

Results: 18 subjects (8 f., 10 m., age 64.2±6.5y) receiving DBS for treatment of PD were included. 8 patients showed psychiatric symptoms starting a few days following the procedure. Edema was absent in all CT scans obtained immediately postoperatively. 14 subjects received an MRI between day 3 and 14 (mean 8.3). Edema surrounding leads was present in 9 cases, of whom 7 showed psychiatric symptoms. Chi-quadrat test shows that the association between edema and psychiatric symptoms was above chance ($p=0.036$).

Conclusion: These findings suggest that edema may be more common than expected and associated with delirium following surgery. As delirium is a known factor promoting later cognitive impairment, identification of risk factors may hold promise in reducing these deficits. This data may help guiding preparations of a multi-centre study addressing associations between postoperative edema, delirum and long-term cognitive deficits in DBS patients.

Disclosure: Nothing to disclose

MS and related disorders 6

P3149

Optical coherence tomography and visual evoked potentials in assessing MS evolution

M. Pisa, G. Di Maggio, S. Guerrieri, R. Santangelo, S. Medaglini, M. Rodegher, B. Colombo, L. Moiola, U. Del Carro, V. Martinelli, G. Comi, L. Leocani
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy

Background and aims: The availability of instrumental markers of myelin and axonal damage to monitor and predict disability progression in MS is fundamental to assess the efficacy of therapeutic interventions. The visual pathway is receiving increasing attention as a putative window into brain neurodegeneration.

Methods: We performed VEPs, OCT with measurement of retinal nerve fiber layer (RNFL) and clinical and neuroradiological assessment at baseline and after an average follow-up of 2 years in 75 subjects with MS of whom 59 were analysed, excluding patients with acute optic neuritis (ON) within 6 months from baseline assessment.

Results: Reduction of binocular mean RNFL thickness was significantly correlated (Spearmann rho - 0.587, $p<0.0001$) with increased rate of the expanded disability status scale (EDSS) regardless of baseline disability, and was greater in subjects with neuroradiological or clinical activity of the disease ($p<0.0001$, test T). The rate of RNFL reduction was similar in eyes with or without previous ON. Although baseline RNFL was correlated with EDSS change at follow-up, this correlation lost significance after correcting for baseline EDSS.

Conclusion: Progressive reduction of RNFL can occur in relation with disease activity along the visual pathway, as detected by VEPs, or as part of the global neurodegeneration process characterizing MS, even with clinical or neurological activity not manifesting with visual symptoms. The association between atrophy of the RNFL and the formation of new inflammatory lesions in the brain could be explained by trans-synaptic degeneration. OCT may be more useful for monitoring neurodegeneration rather than as a prognostic indicator.

Disclosure: Nothing to disclose

P3150

Different MRI measures predict clinical deterioration and cognitive impairment in MS: a 5-year longitudinal study

P. Preziosa[1], M.A. Rocca[1], S. Mesaros[2], M. Copetti[3], M. Petrolini[1], J. Drulovic[2], E. Pagani[1], M. Filippi[1]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]University of Belgrade, Clinic of Neurology, Faculty of Medicine, Belgrade, Serbia, [3]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy

Background and aims: To assess the value of conventional and quantitative brain and spinal cord MRI measures in predicting disability and cognitive worsening in multiple sclerosis (MS) patients after 5 years.

Methods : Brain dual-echo, 3DT1-weighted and diffusion-tensor (DT) MRI scans and cervical cord T2-weighted, 3DT1-weighted and magnetization transfer (MT) MRI scans were obtained at baseline and after 5 years (Y5) in 76 MS patients and 7 controls, followed clinically (EDSS and phenotype changes) and neuropsychologically (Rao's battery). At baseline and Y5, measures of lesion load, brain and cord atrophy were obtained. Brain DT MRI measures of white matter (WM) tracts, normal-appearing WM and gray matter (GM), and cord MT ratio were also assessed. Predictors of clinical and cognitive worsening at Y5 were identified using random forest (RF) analysis.

Results: At Y5, 46/76 patients showed a significant disability worsening (death=9/76), 23/76 evolved to a worse phenotype and 15/61 had a cognitive decline. At Y5, a significant accumulation of brain T2 lesions, brain atrophy (especially for GM), WM tract diffusivity abnormalities and spinal cord atrophy occurred. At RF analysis, baseline WM tract diffusivity measures predicted worsening of clinical disability (classification [C]-index=70%) and phenotype modification (C-index=78%), whereas baseline brain volume, GM diffusivity and cognitive-related WM tract diffusivity abnormalities predicted cognitive worsening (C-index=78%).

Conclusion: Different mechanisms contribute to clinical and cognitive worsening in MS patients after 5 years. While disability deterioration seems mainly due to disruption of WM integrity, cognitive dysfunction is likely due to a complex interplay between WM and GM damage.

Disclosure: Nothing to disclose

P3151

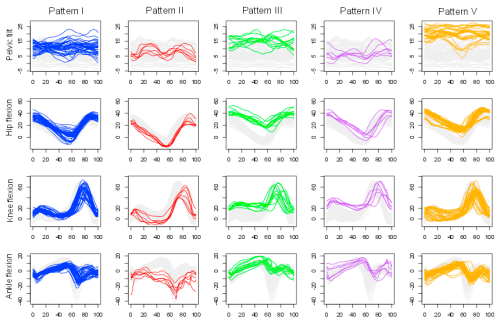
Instrumented gait analysis reveals walking pattern adaptation in patients with primary progressive multiple sclerosis: a hierarchical clustering approach

I. Pulido-Valdeolivas[1], D. Gómez Andrés[1], I. González-Suárez[2], J.A. Martín-Gonzalo[3], I. Rodríguez-Andonaegui[3], C. Oreja-Guevara[2], E. Rausell[1]
[1]Universidad Autónoma de Madrid, Anatomy, Histology and Neuroscience, Madrid, Spain, [2]Hospital Universitario Clínico San Carlos, Neurology, Madrid, Spain, [3]Physiotherapy School. ONCE-UAM, Madrid, Spain

Background and aims: Weight support and translation during gait is poorly managed by patients with primary progressive multiple sclerosis (PPMS), causing disability and dependency. Understanding the way their CNS configures different gait strategies as adaptations to lesion in is essential to design a care plan and to evaluate therapeutic approaches. Our aim is to investigate and describe gait patterns in PPMS patients by means of instrumented gait analysis (IGA) and multivariate statistical approaches.

Methods: 97 kinematic flexion-extension gait cycle graphs of pelvis, hip, knee, and ankle joints were acquired from 10 PPMS patients (48left/49right of each joint). Cycles were classified by hierarchical clustering analysis (dynamic time warping Euclidean distance as dissimilarity measure and average as grouping criterium). The resulting patterns were then compared with graphs obtained from 13 healthy volunteers.

Results: Hierarchical clustering analysis revealed five abnormal walking joint configurations which we named PPMS sagittal patterns I to V. They differ in several degrees of joint adaptation (Figure) in comparison to normalcy (grey lines). Thus, the pelvis tends to be more anteverted, the hip extension tends to deteriorate, the knee joint tends to be more flexed and its maximum flexion in the swing tends to be delayed, or heel strike degrades towards plantigrade or equinus. PPMS patients tend to use invariably the same combination of one or two patterns.



Gait patterns in PPMS patients

Conclusion: The CNS of PMMS patients implements a specific combination of at least five kinematic joint strategies to keep effective walking. Each strategy could emerge from different causal chains that should lead to tailored therapeutic management.

Disclosure: Nothing to disclose

P3152

Switching MS patients from natalizumab to fingolimod therapy: comparison of short and prolonged washout periods

D. Raciborska[1], B. Turner[2], K. Schmierer[3]
[1]Barts and The London School of Medicine and Dentistry, London, United Kingdom, [2]Barts Health NHS Trust, Neurology, London, United Kingdom, [3]Barts and the London School of Medicine and Dentistry, Blizard Institute, Centre for Neuroscience and Trauma, London, United Kingdom

Background and aims: This retrospective study compared clinical outcomes in two groups of MS patients switching from natalizumab to fingolimod. Group 1 had a short interval (SIG) and Group 2 a prolonged interval (PIG) between treatments.

Methods: The total population was 25 patients, the duration of follow-up after the cessation of natalizumab was 17.4 months. The meantime on treatment with fingolimod was 12.8 months (range: 6 to 41 months). The population was divided into SIG (n=15) and PIG (n=10). In SIG the mean treatment interval period was 30 (14-46) days, in PIG it was 179 (76-460) days.

Results: Comparing the two groups over the study period there were more relapses in the PIG group (3 relapses) compared to the SIG group (1 relapse). However no patient had relapses within 6 months in either group and only 1 patient in the PIG had a relapse within 12 months (9 months). None of these differences were significant. There were no significant differences in adverse events between the two groups.

Conclusion: Whilst this is a small study over an 18-month follow-up there was no evidence of any harmful effects of a short interval between natalizumab and fingolimod and a suggestion of fewer relapses. In addition in the whole group the observed 'relapse' or 'rebound' activity after stopping natalizumab is less than published studies. In summary, this study supports the method of rapid initiation of fingolimod treatment following the cessation of natalizumab.

Disclosure: Barts Health and individuals presenting this abstract have received honoraria from Novartis and Biogen.

P3153

Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in caucasian patients

M. Radaelli[1], F. Sangalli[1], L. Moiola[1], M. Rodegher[1], B. Colombo[1], F. Esposito[2], R. Fazio[1], V. Martinelli[1], G. Comi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [2]Scientific Institute San Raffaele, Department of Neurology, Milan, Italy

Background and aims: Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system that generally involves the optic nerve and the spinal cord. Despite the severe prognosis of the disease there are no approved treatments for NMO. The aim of our study was to evaluate the long term safety and efficacy of Rituximab (RTX) in patients affected by NMO and NMO spectrum disorder (NMOsd)

Methods: We evaluated the safety and efficacy of RTX in NMOsd patients who underwent at least one cycle of the drug and with at least 2 years of follow-up.

Results: 21 patients (18 females) were included in the study. At a mean follow-up of 48 months we observed a significant reduction of ARR from 2.0 to 0.16 ($p<0.01$) and of the median EDSS from 5.5 to 4.0 ($p<0.013$). A complete control of the disease was obtained in 57% of patients. 5 patients (24%) reported haematological adverse events consistent with a persistent grade II leucopoenia. Serious infective adverse events were reported by 5 patients. They had leucopoenia and hypogammaglobulinemia, and they all, but one, were wheelchair bound at the beginning of RTX .

Conclusion: In a real world clinical practice a fixed treatment scheme of rituximab with re-treatment every six months is an efficacious treatment for NMO and related disorders with a relative good safety profile. However to assess the best risk-benefit ratio a close monitoring of CD19+ B cells should be performed before re-treatment in patients with high disability and concomitant leucopenia and hypogammaglobulinemia.

Disclosure: Nothing to disclose

P3154

Fampridine modulates thalamic resting state functional connectivity and ameliorates fatigue in multiple sclerosis patients

M.A. Rocca[1], P. Valsasina[2], B. Colombo[3], P. Preziosa[1], V. Martinelli[3], A. Falini[4], G. Comi[3], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, [1]Neuroimaging Research Unit, Milan, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To investigate the effects of fampridine and amantadine on thalamic resting state (RS) functional connectivity (FC) in patients with multiple sclerosis (MS) and fatigue.

Methods: 45 fatigued MS patients were randomly, blindly assigned to undergo treatment with fampridine (n=15), amantadine (n=15) or placebo (n=15) and underwent clinical, neuropsychological (including fatigue assessment) and 3T RS fMRI at baseline (T0) and after four weeks (W4) of treatment. 15 matched healthy controls were also studied. RS FC analysis was done using the left thalamus as seed region and SPM8.

Results: At T0, compared with controls, MS patients showed decreased thalamic RS FC with temporal, occipital, frontal and cerebellar regions. At W4, fampridine patients showed significantly increased global, physical and cognitive MFIS (p=0.003/0.004/0.02), while no significant MFIS changes were observed in amantadine patients. Placebo patients showed improved global, physical and psycho-social MFIS (p=0.02/0.01/0.02). In fampridine patients, increased thalamic RS FC at W4 was detected with bilateral temporal, frontal and parahippocampal regions, while amantadine patients and healthy controls showed no significant RS FC modifications. In placebo patients, small clusters of increased thalamic FC with frontal and parietal regions were identified.

Compared to the other groups, fampridine patients showed a significant RS FC increase over time in the left insula and fusiform gyrus, and right precentral and hyppocampal gyrus. Physical MFIS improvements were associated with increased thalamo-cerebellar FC, while cognitive MFIS improvements were associated with increased thalamo-frontal FC.

Conclusion: Treatment with fampridine ameliorates fatigue in MS patients possibly through a modulation of thalamic functional connections.

Disclosure: Partially supported by a grant from Italian Ministry of Health (GR-2008-1138784).

P3155

Potassium channel Kir4.1: a novel target for neuromyelitis optica autoantibodies?

A. Ruiz, C. Benetollo, S. Cavagna, S. Vukusic, P. Giraudon, R. Marignier

Lyon Neuroscience Research Centre, Lyons, France

Background and aims: Autoantibodies directed against the potassium channel Kir4.1 have been recently identified in the sera of multiple sclerosis (MS) patients. As Kir4.1 is mainly expressed by astrocyte and associated to aquaporin4 at the membrane, we hypothesized that such autoantibodies could also be present in neuromyelitis optica (NMO) patients. Our objectives were to develop a new method for Kir4.1 autoantibodies detection to identify conformational epitopes and to test their interest in a cohort of MS and NMO patients.

Methods and Materials: We set up an in-house method for the detection of Kir4.1 autoantibodies by cell-based assay with live HEK cells transiently transfected with His-Kir4.1. We then tested sera from 56 NMO and 171 MS patients and 19 healthy donors. A proportion of samples were also tested for: i) binding on deglycosylated form of Kir4.1 after Tunikamicin exposure ii) Kir4.1 expression in Western blot after exposure to rat astrocyte primary culture.

Results: A relatively high proportion of NMO patients tested positive for Kir4.1 autoantibodies (16/56, 28.5%), mainly in the AQP4-IgG positive group (13/36, 36%). By contrast, only 3/171 MS sera (1.75 %) were positive. None of the control samples were positive. Deglycosylation did not modify sera binding on Kir4.1. Purified IgG from Kir4.1 autoantibodies positive NMO sera downregulate Kir4.1 astrocyte expression, suggesting a pathogenic effect.

Conclusion: Using a new method for Kir4.1 autoantibodies detection, even though we cannot reproduce the findings on MS, we demonstrated a potential high interest of such autoantibodies in NMO.

Disclosure: Nothing to disclose

P3156

Fatigue during multiple sclerosis relapse: relation to relapse severity

S. Sabanagic-Hajric, E. Suljic, N. Subasic

Clinical Center University of Sarajevo, Department of Neurology, Sarajevo, Bosnia and Herzegovina

Background and aims: Fatigue is defined as subjective lack of physical and/or mental energy perceived by individual. The objective was to investigate presence of fatigue in multiple sclerosis (MS) patients during relapse and its relation to relapse severity.

Methods: This cross sectional study included 120 MS patients during relapse treated at the Department of Neurology, Clinical Center University of Sarajevo. Fatigue was measured by fatigue severity scale (FSS).

Results: Mean FSS score was 4.83±1.49. 45% patients with FSS score≥5.0 were clasiffied as fatigue (MSF) group while 40% patients with FSS≤4.0 were classified as non-fatigue (MSNF) group. There were significant differences in FSS scores between mild (Me=3.7; IQR=2.6 to 5.8) and severe relapse (Me=6.5; IQR=5.0 to 7.0) (p=0.013) and moderate (Me=3.8; IQR=3.2 to 6.1) and severe relapse (p=0.002) (figure 1). There were also significant differences in FSS scores between MSNF (Me=2.7; IQR=2.5 to 3.5) and MSF groups (Me=6.0; IQR=5.0 to 7.0) (P=0.002) in patients with mild relaps; MSNF (Me=3.3; IQR=3.0 to 3.5) and MSF groups (Me=6.1; IQR=5.5 to 6.5) (p<0.001) in patients with moderate relaps; MSNF (Me=3.5; IQR=2.8 to 4.0) and MSF groups (Me=7.0; IQR=5.8 to 7.0) (p=0.002) in patients with severe relapse (figure 2). Regression analysis showed that relaps severity didn't independently predict fatigue severity (table 1).

Figure 1. Fatigue severity scale (FSS) scores in multiple sclerosis patients by relaps severity

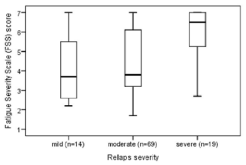


Figure 1.

Figure 2. Fatigue severity scale (FSS) scores in fatigue (MSF) and non fatigue (MSNF) multiple sclerosis patients by relaps severity

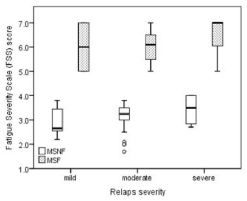


Figure 2.

Table 1. Multivariate regression analysis: predictors of fatigue severity in multiple sclerosis patients during relapse

Variables	B	SE_B	β
Intercept	1.230	0.563	
EDSS score	0.319	0.077	0.336**
BDI score	0.076	0.017	0.380**
Disease duration	-0.031	0.022	-0.109
Gender	-0.146	0.223	-0.045
Age	0.028	0.011	0.202*
Relaps severity	0.146	0.200	0.055

Note: ** p <0 .001; * p < 0.05,

B = unstandardized regression coefficient; SE_B = Standard error of the coefficient;

β = standardized coefficient

Table 1.

Conclusion: Fatigue is a frequent symptom during multiple sclerosis relapse. It should be recognized and treated as other disabling symptoms of multiple sclerosis. Higher fatigue severity relation to higher relapse severity is partially due to influence of other factors such as disability, depression and patient's age.

Disclosure: Nothing to disclose

P3157

RETURN II: Investigation of clinical disease and safety outcomes in RMS-patients receiving subcutaneous (sc) interferon (IFN) beta-1a following discontinuation of natalizumab

R. Weissert[1], K. Jendroska[2], T. Wagner[3]

[1]Klinik und Poliklinik für Neurologie, Regensburg, Germany, [2]Facharzt für Neurologie, Berlin, Germany, [3]Merck Serono GmbH, Darmstadt, Germany

Background and aims: After discontinuation of an escalation therapy, limited data are available regarding switches to first-line therapies. Therefore this non-interventional study focused on patients with relapsing multiple sclerosis (RMS) receiving subcutaneous (sc) interferon (IFN) beta-1a after treatment with natalizumab.

Methods: Patients with RMS who had been treated with natalizumab and switched to sc IFN beta-1a treatment were observed for 24 months. Seven follow-up visits were scheduled following the baseline visit. The primary endpoint was annualized relapse rate (ARR) over 24 months. Tolerability of sc IFN beta-1a was rated on a 4-point scale by physicians at the final visit.

Results: Evaluable data were available for 21 patients from nine centres. All patients had received first-line disease-modifying drugs prior to starting natalizumab. In 15 (71.4%) patients, high relapse rate was cited as the reason to start natalizumab. The mean duration of natalizumab therapy was 24.4 months. 14 (66.7%) patients discontinued study treatment with sc IFN beta-1a (mean treatment duration: 8.7 months). During the observation period, 15 (71.4%) patients experienced at least one relapse; the mean ARR for the whole cohort was 1.1. 15 patients had at least one adverse drug reaction. 'Headache' was the most common preferred term. No serious adverse events were reported. Tolerability was rated as 'very good' or 'good' for 16 (76.2%) patients and 'not satisfactory' in 3 (14.3%) who also discontinued treatment prematurely.

Conclusion: Disease activity was stabilized on a moderate inflammatory level after natalizumab treatment, especially compared to the inflammatory level before escalation therapy.

Disclosure: Study supported by: Merck Serono GmbH, Darmstadt, Germany

Neurogenetics 3

P3158

Novel SEPT9 mutation underlying Hereditary Neuralgic Amyotrophy: multigenerational evaluation and phenotypic variability

S.P. Iyadurai[1], J. Roggenbuck[2], J. Kissel[1]
[1]OSU, Neurology, Columbus, USA, [2]OSU, Genetics, Columbus, USA

Three mutations in SEPT9 have been described to date that underlie HNA. Here, we report a novel SEPT9 mutation and the variability of expression of hereditary neuralgic amyotrophy (HNA) in a multi-generational family.

Methods: Case Series

Results: The proband, a 54-year-old man presented with right arm weakness preceded by pain approximately 2 weeks prior. He reported that many of his family members had had a similar episode at variable ages, and with varying degrees of weakness. Some of them had experienced sequential and/or recurrent asymmetric weakness in the upper extremities. Neurological examination revealed normal cranial nerves, scapular winging, asymmetric proximal weakness, hyporeflexia and normal lower extremity examination. MRI of brachial plexus revealed enhancement of the T1 nerve root. EMG/NCS revealed bilateral brachial plexopathy. Gene testing revealed a novel aberration in the SEPT9 gene (38 Kb duplication with a proximal breakpoint in the exon 2 of SEPT9). Clinical evaluation and medical history of family members revealed varying ages on onset, different patterns of muscle involvement and recurrence and hypotelorism in all the affected members.

Conclusion: We report a novel SEPT9 mutation in a multigenerational family with HNA and its clinical variability. Hypotelorism and recurrent painful brachial plexopathy seem to be invariant features associated with this novel mutation.

Disclosure: Nothing to disclose

P3159

Identification of novel mutations in LRRK2 gene in patients with Parkinson's disease

M. Janković, N.D. Kresojevic, V. Dobricic, V. Marković, I. Petrović, I. Novakovic, V.S. Kostic
Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia, Belgrade, Serbia

Background and aims: Mutations in LRRK2 (leucine - rich repeat kinase 2) are the most common cause of autosomal dominant Parkinson's disease (PD). Large international studies have revealed that pathogenic mutations are clustered in several exons coding for functional domains of LRRK2 protein, but the mutation frequency differs among populations. Systematic study of LRRK2 mutation prevalence and phenotype in Serbian population has not been performed.

Methods: Comprehensive mutation screening of selected exons of LRRK2 gene, harboring proven and potential pathogenic mutations, was performed in 486 Serbian PD patients.

Results: Previously reported LRRK2 mutations I1371V and G2019S were identified in a single patient each, and c.4536+3A>G substitution in two patients. G2019S is the most common, proven pathogenic mutation, while pathogenic roles for recurrent variants I1371V and c.4536+3A>G are possible, but not confirmed. Two novel LRRK2 mutations S1508G and I1991V were also discovered in 2 unrelated patients. These mutations are considered as disease causing according to software predictions, but additional segregation and functional analyses are required.

Conclusion: Mutation frequency in our study (1.23%) was similar to other European populations, although the most common mutations were underestimated and novel variants were detected. In most cases, symptoms of LRRK2-PD are similar to sporadic PD, so estimation of frequency and penetrance of mutations in different populations is important for efficient genetic testing strategy and counseling.

Disclosure: This study was supported by grants from the Ministry of Education and Science of Republic of Serbia (ON175090 and ON175091).

P3160

Strong HLA-DPB1*03:01 association with multiple sclerosis risk in patients of a Hellenic cohort study.

M. Anagnostouli[1], S. Katsavos[1], A. Artemiadis[2]
[1]Medical School, Athens National and Kapodistrian University, Aeginition Hospital, Immunogenetics Laboratory, of 1st Dept of Neurology, Athens, Greece, 2417 General military hospital nimts, neurology, Athens, Greece

Background and aims: Multiple Sclerosis (MS) is an autoimmune and degenerative disease, mainly affecting young adults. There are multiple, independent correlations with MS risk across the Major Histocompatibility Complex, with predominant the Human Leucocyte Antigen (HLA) DRB1*15:01 allele association, already confirmed in many Caucasian populations, the Hellenic included. Nevertheless, the DP region has not been investigated as thoroughly as the DR/DQ region in this context. Aim of this study was to perform, for the first time, DPB1* genotyping for MS patients of Hellenic origin.

Methods: 70 patients suffering from MS, followed in our Outpatient Clinic, and 246 healthy controls were included in this study. HLA-genotyping was performed by Sequence Specific Oligonucleotide (SSO) technique. Statistical processing included univariate analyses with chi-squared tests (level of significance set at p=0.05).

Results: Our patients were predominantly women (64.3%), with mean age 38.1 years, and mean age of MS onset 29.6 years. DPB1*03:01 allele frequency was significantly increased in MS patients compared to controls (p=0.001). There were also trends towards increase of the DPB1*10 and DPB1*14 alleles and towards reduction of DPB1*13 and DPB1*17 alleles. Interestingly, no coexistence of DRB1*15:01 and DPB1*03:01 was found in any patient of our sample.

Conclusion: Although DRB1*15:01 allele has an established role in MS, there is inadequate information concerning the impact of DPB1* region in MS genetic burden. Our observations are in accordance with recent studies, regarding increased DPB1*03:01 frequency in Caucasian MS patients. Its effects are probably independent of these attributed by other susceptibility alleles, like the predominant DRB1*15:01.

Disclosure: Nothing to disclose

P3161

Connecting genes to pathways and networks in neurodegenerative diseases

P. Kuru, P.H. Ozdinler
Northwestern University Feinberg School of Medicine, Department of Neurology, Chicago, USA

Background and aims: The goal of this study is to investigate the link between genes, proteins, and networks in an effort to understand the cellular and molecular basis of selective vulnerability in neurodegenerative diseases. To identify the networks and cellular pathways that are affected we focus on the binding partners of the proteins that are encoded by the mutated genes. Our studies will reveal both the canonical pathways and cellular networks that are particularly significant for different neurodegenerative diseases.

Methods: Using genes that lead to Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) when mutated, we first identified their binding partners and performed systems analysis to reveal the canonical pathways and cellular networks they are critically important.

Results: Glucocorticoid Receptor Signaling is the main canonical pathway in AD, ALS and FTD. HNF4A interacts with 11 different proteins in the ALS, whereas it interacts with only 3 proteins in the AD connectivity map. Likewise, APP interacts with 17 proteins in the AD, but with only 2 proteins in the ALS domain. Such differences are exceptionally important to suggest the protein connectome and to reveal potential candidate molecules/genes/targets for the initiation of neuronal vulnerability and for selective neuron death. Investigation of protein-protein interactions reveal the potential pathways that are affected in distinct neurodegenerative diseases.

Conclusion: Selective gene expression profile in neurons inform us about their potential vulnerability and the pathways that are particularly important for their function and connectivity. This information will shed light onto the common and unique mechanisms involved for different neurodegenerative diseases.

Disclosure: Nothing to disclose

P3162

Autosomal recessive ataxia due to ADCK 3 mutation – a series of 3 cases from 2 families.

S. Little, J. Flowers, M. McEntagart, S. Omer
St Georges Hospital, London, UK, Atkinson Morley Neurosciences centre, London, United Kingdom

Background and aims: Autosomal recessive cerebellar ataxias (ARCAs) are clinically and genetically heterogeneous. They lead to a progressive cerebellar dysfunction, often in association with a variety of other neurological symptoms and signs. Recently, a new genetic locus has been discovered for ARCAs in a gene responsible for Co-enzyme Q10 synthesis, namely the AarF domain containing kinase 3 gene (ADCK3). This gene is responsible for encoding a membrane protein involved in electron transfer within the mitochondrial respiratory chain complex. Importantly, this condition can potentially respond to Co-enzyme Q10 supplementation, making its recognition amongst the ARCAs particularly important. However, clinical identification is complicated by the wide range of phenotypic presentations that can occur.

Methods: Here we describe a case series of 3 patients with cerebellar ataxia and genetically proven ADCK3 mutations from our centre.

Results: Two siblings presented with highly similar phenotypes of childhood onset cerebellar ataxia, myoclonus and bradykinesia are compared with a further case characterised by cerebellar ataxia, seizures and a different ADCK3 mutation.

Conclusion: The clinical identification, diagnostic work up, genetic testing and management of this condition is discussed.

Disclosure: Nothing to disclose

P3163

Cerebral folate deficiency (CFD) in adult patients: a treatable non-specific syndrome associated with various diseases.

M. Masingue[1], J.-F. Benoist[2], F. Sedel[3], E. Roze[1], Y. Nadjar[3]
[1]*Hôpital Pitié-Salpêtrière, Department for Diseases of the Nervous System, Paris, France,* [2]*Hôpital Robert Debré, Department of Biochemistry and Hormonology, Paris, France,* [3]*Hôpital Pitié-Salpêtrière, Department for Diseases of the Nervous System, UF Neuro-metabolic, Paris, France*

Background and aims: Cerebral folate deficiency (CFD) is characterized as any neuro-psychiatric condition associated with low cerebrospinal fluid (CSF) level of 5-methyltetrahydrofolate (5MTHF). Mainly described in children, it can be associated with numerous diseases. We describe clinical and radiological data in adult patients with CFD, as well as evolution after folinic acid supplementation.

Methods: A retrospective study was conducted in patients for whom 5MTHF was examined in CSF. Demographic, clinical, biological, radiological and treatment data were recorded. CFD was defined as a 5MTHF level below 41mmol/L in CSF.

Results: Among 224 patients, 69 had CFD (31%), with a mean 5MTHF level of 21 nmol/L (±11, 2-40) and a mean age at onset of 24 years (±21, 0-65). 35% of CFD patients had a defined underlying condition. Fahr disease (n=7), CAFSA (Cerebellar Ataxia with elevated cerebrospinal Free Sialic Acid) syndrome (n=4), and hepatic encephalopathy (n=16) were associated with the lowest 5MTHF levels. In CFD patients, cognitive impairment was more common (44.6% vs 28.8%, p= 0.024), as was hearing loss (18.5% vs 6.9%, p=0.011). Calcifications and T2 hypersignals in posterior fossa were more frequent (respectively 29% vs 2.2%, p= 0.014 and 16.3% vs 4.8%, p=0.021). 25 patients received folinic supplementation and 13 showed clinical improvement, mostly on gait disturbance (n=7), movement (n=7) and behavior (n=5) disorders. 5MTHF in CSF had normalized after treatment in 8 over 9 cases.

Conclusion: CFD has a large clinical and radiological spectrum in adult patients, and is associated with various diseases. In severe CFD, folinic acid treatment may dramatically improve clinical condition.

Disclosure: Nothing to disclose

P3164

Mutations in the genes of the α-ketoglutarate dehydrogenase may predispone to Alzheimer's disease

M.J. Molnár[1], E. Bányász[2], K. Pentelényi[2], V. Hársfalvi[2], M. Palkovits[3], V. Ádám-Vizi[4]

[1]Semmelweis University, [3]Department of Genomic Medicine and Rare Disorders, Budapest, Hungary, [2]Semmelweis University, Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary, [3]Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Budapest, Hungary, [4]Semmelweis University, Department of Medical Biochemistry, Budapest, Hungary

Background and aims: The αKGDH enzyme is a key enzyme of the Krebs cycle and its mutations are known to result in extensive oxidative stress and cell damage. The hereditary mutations lead to a variety of phenotypes, extending from the lethal infant-type enzyme defect, to the elderlys' chronic diseases. Reduced enzyme activity has been reported in Alzheimer's patients' fibroblasts. Our objective was the analysis of the enzyme's genetic code and the incidence of SNP-s in Alzheimer patients.

Methods: In 22 Alzheimer cases DNA from blood samples, in 11 cases from post mortem brain tissue and in 2 control brain samples the E2 and E3 components of the αKGDH: dihydrolipoamide S-succinyltransferase (DLST) and dihydrolipoyl dehydrogenase (DLD) genes were sequenced.

Results: 4 pathogenic mutations were present in 3 of 11 Alzheimer patient's brains: Arg263His missense mutation in DLD gene, Pro204Leu, Leu394Met and Leu453His missense mutations in DLST gene. No mutations were present in the blood samples.

Conclusion: The presence of the 4 pathogenic mutations in the aKGDH may indicate that this enzyme is a keyplayer in the pathogenesis of the Alzheimer's disease. Further studies are needed to support our hypothesis.

Disclosure: Nothing to disclose

P3165

A clinical multimodal approach in a large Italian cohort with Hereditary Spastic Paraplegia (HSP) looking for neurophysiological biomarkers

O. Musumeci[1], V. Rizzo[1], M.T. Bassi[2], M. Marino[1], F. Montagnese[1], A. Quartarone[1], A. Toscano[1]

[1]University of Messina, Messina, Italy, [2]IRCCS Medea, Bosisio Parini, Italy

Background and aims: Hereditary spastic paraplegias (HSP) are a group of neurodegenerative disorders characterized by an extreme clinical and genetic variability. A growing number of testable genes, associated with HSP, offers very large opportunities for their genetic definition but complicates the diagnostic workout. Aim of this study was to present the clinical and electrophysiological data in a cohort of HSP patients to identify possible neurophysiological markers capable to better address diagnosis.

Methods: Since 2009, we have recruited over 160 patients with suspected HSP. All patients were evaluated with a standardized clinical protocol. For the molecular definition, 10 genes associated with the more common HSPs were tested. A multimodal electrophysiological protocol, including electromyography (EMG) and nerve conduction study (NCS), motor-evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) at four limbs, visual (VEPs) and brainstem evoked potentials (BAEPs) was applied

Results: A wide variation in age of onset and disease severity was observed among pure and complicated cases and, even, within families. Molecular definition was obtained in 33 patients (21%) (22 SPG4, 4 SPG5,2 SPG10, 3 SPG11, 1 SPG7, 1 SPG15). The common neurophysiological finding was the increased central motor and sensory conduction time at lower limbs. Alterations in VEPs/BAEPs were observed in few cases of SPG4, 5, 11 and 15. Axonal polyneuropathy was detected in SPG5, 10, 11.

Conclusion: Our data confirm the clinical heterogeneity of these disorders. Electrophysiological evaluation in different SPGs showed a various CNS and PNS involvement either in pure or in complicated forms that could be useful to address the molecular diagnos

Disclosure: Nothing to disclose

P3166

Natural history of cerebrotendinous xanthomatosis: a pediatric disease diagnosed in adults.

Y. Nadjar[1], P. Couvert[2], F. Lamari[3], M.D.M. Amador[1], E. Flammand-Roze[1], B. Degos[1], F. Mochel[4]

[1]Hôpital Pitié Salpétrière, Département des maladies du Système Nerveux Central, UF Neurométabolique, Paris, France, [2]Hôpital Pitié Salpétrière, Laboratoire de Biochimie Endocrinienne et Oncologique,, Paris, France, [3]Hôpital Pitié Salpétrière, Biochimie Métabolique, UF Neurométabolique, Paris, France, [4]Hôpital Pitié Salpétrière, Département de Génétique, UF Neurométabolique, Paris, France

Background and aims: Cerebrotendinous xanthomatosis (CTX) is a treatable inborn error of metabolism for which the onset of neurological symptoms usually occurs in young adults. Elevated plasma cholestanol is a specific biomarker of the disease. Here we describe the natural history of CTX in our population. We aimed at identifying early clinical markers allowing treatment initiation before the occurrence of irreversible neurological disability.

Methods: We conducted a retrospective clinical study on 17 French patients with CTX. We collected demographic, clinical, electrophysiological and radiological data.

Results: Neurological symptoms occurred at a mean age of 28 years (15-50), and consisted of gait abnormalities (61%), cognitive and/or behavioral disorder (25%, excluding learning difficulties), or both (14%). Gait abnormalities comprised mixed cerebellar and pyramidal dysfunction (43%), isolated cerebellar ataxia (28%), isolated pyramidal dysfunction (14%), or peripheral nerve impairment (14%). Cognitive and psychiatric symptoms consisted mainly of frontal syndrome with disinhibition and aggressive behavior. 47% of patients had juvenile bilateral cataract preceding the occurrence of neurological symptoms, 64% had chronic diarrhea in early childhood, and 80% had learning difficulties in childhood or adolescence.

Conclusion: Overall, 88% of patients had early clinical markers of the disease (cataract and/or chronic diarrhea and/or learning difficulties) during childhood. However, CTX was mainly diagnosed when patients were adults. Therefore, the identification of early clinical markers of CTX, as described here, should prompt the dosage of plasma cholestanol. The early initiation of CTX treatment (CDCA : chenodeoxycholic acid) could indeed prevent or delay the occurrence of neurological symptoms.

Disclosure: Nothing to disclose

Neuroimmunology 2

P3167

Optical coherence tomography in patients with radiologically isolated syndrome

R. Karabudak[1], A. Vural[1], N.P. Acar[1], M.A. Tuncer[1], G. Sayat[1], S. Kadayifcilar[2], A. Kurne[1]
[1]Hacettepe University, Neurology, Ankara, Turkey, [2]Hacettepe University, Opthalmology, Ankara, Turkey

Background and aims: Incidental detection of white matter lesions is named as radiologically isolated syndrome (RIS). Some of these patients develop multiple sclerosis (MS) in time. In MS brains, axonal injury was observed in normal appearing white matter and retinal nerve fiber layer (RNFL) of the unaffected eye. Retinal axonal loss begins early in the course of MS. In the absence of clinically evident optic neuritis, RNFL thinning was detected in patients with clinically isolated syndrome. There is no study of acknowledged axonal injury in RIS subjects. In this study, we investigated whether axonal trans-section occurred in retinal layer of the RIS subjects.

Methods: We present the preliminary data of an ongoing, prospective study. Spectral-domain optical coherence tomography (SD-OCT) is performed to measure RNFL thickness and macular volume (MV) in individuals fulfilling 2009 Okuda Criteria and healthy controls.

Results: SD-OCT has been done in both eyes of 12 RIS subjects (7 female, 5 male) and 12 controls. Overall RNFL thickness and MV were not statistically different between groups. When taken individually, atrophy of RNFL was detected in one subject and borderline RNFL thickness was detected in retina of 6 more subjects compared to the general population, whereas in the control group the measurements were between normal limits.

Conclusion: These data suggest that axonal transection in retina might be elicited in RIS subjects. SD-OCT may reveal subclinical retinal axonal loss at the earliest stages of MS. Whether there might be an apparent consistency between brain MRI -DTI and retinal OCT will be the next analysis of this study.

Disclosure: This study is supported by Merck-Serono.

P3168

Multiparameter autoantibody screening in the diagnosis of neurological autoimmune diseases

W. Stöcker, C. Probst, B. Teegen, K. Rentzsch, W. Schlumberger, J. Fraune, L. Komorowski
Institute of Experimental Immunology, Euroimmun AG, Lübeck, Germany

Background and aims: The aspect of autoimmunity in neurological disorders attracts a steadily growing interest. Identified autoantibodies include those against intracellular antigens (biomarkers of paraneoplastic neurological syndromes) and newly, those against neuronal cell surface proteins, many of them being pathogenic in several forms of autoimmune encephalitis. However, differential diagnosis of the clinical conditions is challenging due to similar symptomatic appearances and often requires consideration of a broad range of anti-neuronal antibodies. Here, we report on diagnostic benefits of determining a comprehensive antibody profile by multiparametric testing during requested sample analyses.

Methods: 16,741 samples were sent to the Clinical Immunological Laboratory (Lübeck) from April 1st 2012 until March 31st 2013. Irrespective of the parameter requested, all samples were tested for multiple parameters using indirect immunofluorescence on BIOCHIP-mosaics (combining various substrates in one reaction field) and immunoblot.

Results: 14.1% of the samples were positive for at least one neurological parameter. About half of the detected autoantibodies (52.1%) were of the IgG class. Among these, antibodies against extracellular antigens were twice as frequent as antibodies against intracellular antigens. 53.4% of the samples were positive for the requested parameter whereas 46.6% of the samples were positive for another but requested parameter.

One neurological parameter positive	13.6%
Two or more neurological parameter positive	0.5%
Fraction of IgG among detected autoantibodies	52.1%
Fraction of IgA, IgM, C3c among detected autoantibodies	47.9%
IgG positive for requested parameter	53,4%
IgG positive for not requested parameter	46,6%

Table 1: Results of multiparametric screening, samples with request on analyses of one or more neurological autoantibodies, n = 16,741 (April 1st, 2012 – March 31st, 2013).

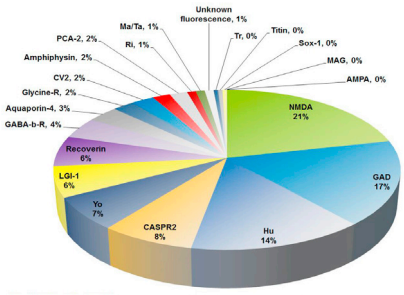


Figure 1: Composition of detected autoantibodies of class IgG in samples which have been sent with request on analyses of neurological parameters.

Conclusion: Our results reveal that multiparametric screening of samples can increase the hit rate of positive and diagnostically relevant findings by 87% compared to single testing of requested parameters. This may also accelerate the diagnostic process. Both aspects significantly support correct and rapid diagnoses of neurological autoimmune diseases, which is crucial to initiate appropriate and often life-saving therapies.

Disclosure: Research has been performed at the Clinical Immunological Laboratory Prof. Dr. med. Winfried Stöcker, Lübeck in research cooperation with EUROIMMUN AG.

P3169

Prevalence of autoreactive antibodies (ARAB) in patiens with relapsing-remitting multiple sclerosis (RRMS) under interferon beta treatment.

C. Papastergios[1], E. Karamouzos[1], I. Markakis[1], C. Kaliouli[2], E. Pappa[2], G. Gekas[1]

[1]"St. Panteleimon" General State Hospital of Piraeus, Neurology, Piraeus, Greece, [2]"St. Panteleimon" General State Hospital of Piraeus, Immunology, Athens, Greece

Background and aims: Interferon beta is widely used as a first line immunomodulatory medication for patients with RRMS. However, interferon treatment has been implicated in the development of autoimmune disorders. Our objective was to evaluate the impact of interferon beta-1a and beta-1b treatment on the serum autoantibody profile of patients with RRMS.

Methods: 61 patients with newly diagnosed RRMS were followed-up during a 2 year period, after the initiation of immunomodulatory treatment with interferon (interferon beta-1a: 37, interferon beta-1b: 24). Patients were tested for an extensive panel of ARAB including antinuclear (ANA), thyroid microsomal (anti-TPO), human thyroglobulin (anti-TG), smooth muscle (ASMA), anticardiolipin (aCL), anti-beta2-glycoprotein-1 (anti-beta2-GP1) and anti-neutrophil cytoplasmic antibodies (ANCA). Serological tests were performed at baseline and at the end of the 2-year follow-up

Results: Interferon beta-1a treatment was associated with a statistically significant increase in ARAB positivity for ANA, ASMA, aCL, ANCA; alterations of anti-TPO, anti-TG, anti-beta2-GP1 and anti-Ro were not statistically significant. Moreover, patients having positive ANA at baseline, showed a statistically significant rise of serum titers following treatment ($p<0.01$). Interferon beta-1b treatment, was not associated with significant induction of any ARAB, nor with significant alterations of ARAB titers in patients that were positive at baseline.

Conclusion: Interferon beta-1a may induce ARAB formation in patients with RRMS and thus seems to have a greater risk of autoimmunity induction.

Disclosure: Nothing to disclose

P3170

Expression of the quiescence marker, TOB-1, in T-cells of CIS patients at high risk of rapid conversion to clinically definite MS

S. Basdeo[1], S. Kelly[2], K. O'Connell[2], N. Tubridy[2], M. Hutchinson[2], J. Fletcher[1], C. McGuigan[2]
[1]Trinity College Dublin, Schools of Medicine and Biochemistry & Immunology, Dublin, Ireland, [2]St Vincent's University Hospital, Department of Neurology, Dublin, Ireland

Background and aims: There are no laboratory biomarkers to accurately identify patients at risk of rapid conversion to clinically definite multiple sclerosis (CDMS) following a clinically isolated syndrome (CIS). CD4+ T-cells play a central role in the pathogenesis of MS. A recent study identified a pattern of gene expression that distinguished CIS patients with rapid conversion to CDMS. TOB-1, which plays a crucial role in maintaining T-cell quiescence, was reduced in patients with rapid conversion whilst CD44, the osteopontin receptor, was over-expressed in this group.
Methods: Expression of TOB-1 and CD44 in total and naive CD4+ T-cell from PBMC was examined by RT-PCR in patients converting from CIS to CDMS within 1 year (n=10), those not converting within 1 year (n=10) and patients with an aggressive course on Tysabri (n=5), compared with healthy controls (n=10).
Results: No significant difference in expression of TOB-1 or CD44 was seen between groups. There was a trend towards reduced TOB-1 expression in total CD4+ T-cells from patients converting to CDMS within 1 year compared with those not converting. Naive CD4+ T-cells from patients with aggressive MS exhibited reduced TOB-1 expression compared with the other groups analysed, however, this was not statistically significant.
Conclusion: CD4+ T-cell expression of TOB-1 was not significantly reduced in patients who progressed from CIS to CDMS within 1 year in this study. TOB-1 with other markers of T cell quiescence may predict a cohort of patients at risk of a more aggressive disease course.
Disclosure: Nothing to disclose

P3171

Limbic encephalitis and intrathecal immunoglobulin A and G antibodies to Synapsin, a neuron-specific synaptic vesicle-associated protein

J. Piepgras[1], M. Höltje[2], C. Otto[3], H. Harms[3], F. Benfenati[4], A. Pich[5], D. Gitler[6], G. Ahnert-Hilger[2], K. Ruprecht[1]
[1]Charité Universitätsmedizin Berlin, Department of Neurology, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Institute for Integrative Neuroanatomy, Berlin, Germany, [3]St. Josefs-Krankenhaus, Klinik für Neurologie, Potsdam, Germany, [4]Istituto Italiano di Tecnologia, Department of Neuroscience and Neurotechnologies, Genoa, Italy, [5]Hannover Medical School, Institute for Toxicology, Hanover, Germany, [6]Ben-Gurion University of the Negev, Department of Physiology and Cell Biology, Beer-Sheva, Israel

Background: Limbic encephalitis (LE) is characterized by memory dysfunction, seizures, behaviour changes, and mesiotemporal involvement on imaging studies, and is associated with antibodies to neuronal autoantigens. Here we report the identification of the synaptic vesicle-associated protein Synapsin as a novel autoantigen in a patient with LE.
Methods: Methods included indirect immunofluorescence, immunoprecipitation, mass spectrometry, cell-based assays with Synapsins Ia, Ib, and IIa plasmids, and immunoblots of wild-type and Synapsin I/II/III null mice.
Results: A 70-year-old patient presented with seizures, short-term memory deficits, and left hippocampal hyperintensities on T2-weighted magnetic resonance imaging. Cerebrospinal fluid (CSF) studies revealed a strong intrathecal synthesis of immunoglobulin (Ig)A and IgG. Except for low-titre IgG antibodies to voltage-gated potassium channels in CSF, testing for known neuronal autoantibodies was negative. However, indirect immunofluorescence on murine brain sections showed prominent staining of the mossy fibre tract, amygdala, and the cerebellar molecular and granular layer by IgA antibodies in the patient's CSF and serum. Immunoprecipitation with CSF IgA and subsequent mass spectrometry identified the neuron-specific synaptic vesicle-associated protein Synapsin as the antigenic target. Knockout studies and cell-based assays unambiguously confirmed Synapsin Ia/Ib and Synapsin IIa as autoantigens detected by intrathecally synthesized IgA and IgG antibodies.
Conclusion: Synapsin is a novel autoantigen in LE. Remarkably, in addition to IgG, Synapsin is targeted by intrathecally produced IgA, suggesting that also IgA antibodies could play a role in antineuronal autoimmunity. Future studies should clarify the prevalence and pathogenic relevance of IgA and IgG antibodies to Synapsin in patients with LE.
Disclosure: Nothing to disclose

P3172

Neuropsychiatry and onconeuronal antibodies: An observational cohort study of 585 patients admitted to acute psychiatric care

S.G. Saether[1], M. Schou[1], A.E. Vaaler[1], K. Borowski[2], B. Teegen[2], D. Kondziella[3], W. Stoecker[2], S.K. Reitan[1]
[1]St Olavs University Hospital, Department of Psychiatry, Trondheim, Norway, [2]Institute for Experimental Immunology, Affiliated to EUROIMMUN AG, Lübeck, Germany, [3]Rigshospitalet, Copenhagen University Hospital, Department of Neurology, Copenhagen, Denmark

Background and aims: Paraneoplastic limbic encephalitis frequently presents with prominent psychiatric symptoms. Onconeuronal antibodies are used as serum markers of paraneoplastic limbic encephalitis. The significance of these antibodies in patients with psychiatric syndromes but without a limbic encephalitis is unknown. We aimed at examining the prevalence of onconeuronal antibodies in patients acutely admitted to psychiatric care. We hypothesized that onconeuronal antibodies are frequent in this population and that different antibodies are associated with distinct neuropsychiatric profiles.

Methods: Serum collected from 585 consecutive patients admitted to acute psychiatric care was assessed for the presence of Immunoglobulin (Ig)G, IgM and IgA onconeuronal antibodies. Analysis was performed with an indirect immunofluorescence test (Euroimmun; Lübeck, Germany).

Results: We identified 31 patients (5.3%) with positive onconeuronal antibody titres. 19 patients (3.2%) had anti-Ma2 antibodies (6 IgM, 6 IgA and 7 IgG), and 9 patients (1.4%) had anti-Ma1 antibodies (0 IgM, 2 IgA and 7 IgG). Anti-Yo (n=3 patients), anti-Amphiphysin (n=2) and Rho GTPase (n=1) antibodies were less frequent. We found a trend towards a higher prevalence of high titres of anti-Ma2 antibodies in the ICD 10 F20 diagnostic group (schizophrenia, schizotypal and delusional disorder) as compared with the other diagnostic groups (p=0.019).

Conclusion: Compared to healthy blood donors (Dahm et al. 2014), we identified a relatively high prevalence of anti-Ma2 antibodies in patients with acute psychiatric symptoms, in particular in those with psychotic syndromes. The present results suggest that further research into the significance of onconeuronal antibodies for neuropsychiatry phenomenology is warranted.

Disclosure: W.S. is shareholder of Euroimmun AG and member of the Board of Euroimmun AG. K.B. and B.T. are employees of Euroimmun AG.

P3173

Serum prevalence of N-methyl d-aspartate receptor (NMDAR) antibodies in an unselected cohort of patients with acute psychiatric symptoms

M. Schou[1], S.G. Saether[1], S.K. Reitan[1], K. Borowski[2], B. Teegen[2], D. Kondziella[3], W. Stoecker[2], A.E. Vaaler[1]
[1]St Olavs University Hospital, Department of Psychiatry, Trondheim, Norway, [2]Institute for Experimental Immunology, Affiliated to EUROIMMUN AG, Lübeck, Germany, [3]Rigshospitalet, Copenhagen University Hospital, Department of Neurology, Copenhagen, Denmark

Background and aims: Patients with NMDAR encephalitis typically present with prominent psychiatric symptoms, especially psychosis, before they develop neurological symptoms. In an unselected cohort of patients admitted to acute psychiatric care we hypothesized that patients with psychotic disorders had a higher prevalence of serum NMDAR antibodies compared to other patients.

Methods: Serum collected from an unselected cohort of 926 patients admitted to acute psychiatric care at the Department of Psychiatry, St Olavs Hospital, Trondheim, Norway were used. Patients with ICD-10 diagnosis F20-F29, psychotic disorders, were compared to the other patients, see table 1. Antibody analysis was performed with an indirect immunofluorescence test (Euroimmun; Lübeck, Germany).

Results: 70 patients (7.6%) had NMDAR antibodies of Immunoglobulin (Ig)G, IgM or IgA subtype. 5 patients were positive for Ig G, 38 for Ig M and 34 for Ig A NMDAR antibodies. The prevalence of NMDAR antibodies in patients with psychotic disorders were 6.3% and did not differ significantly from patients with other diagnosis leading to acute psychiatric admissions (7.8% (Chi square 0.226 p=0.64)). Including only high antibody titers (1:100 and above) in our analysis, the prevalence still did not differ in the two groups (2.1% and 3.1%, respectively. Fisher exact p=0.78).

	Psychotic disorders §	Non psychotic disorders*
N (number of patients)	144	782
Age, mean (sd)	43 (14,4)	40 (16,5)
Sex, Male %	52,8	48,6
NMDA		
N seropositives (%)	9 (6,3)	61 (7,8)
N seropositive males	3	26
Ig class (M/A/G)	5/5/0	33/29/5
Titer range	1:10-1:320	1:10-1:3200

§ ICD 10 F20-29, schizophrenia, delusional disorders, acute psychosis and schizoaffective disorders.
*organic-, substance use-, affective-, neurotic and anxiety-, personality-, and other disorders.

Table 1 Prevalence of NMDAR antibodies in patients with psychotic and non-psychotic disorders

Conclusion: We did not find any significant differences in serum prevalence of NMDAR antibodies between patients with psychotic disorders and other patients. Positive NMDAR IgG antibody titre status was rare. However, further studies on whether or not the antibodies are of clinical significance in patients with psychiatric disorders are needed.

Disclosure: K.B and B.T. are employees of Euroimmun AG. W.S. is shareholder and member of the Board of Euroimmun AG.

P3174

Association of a FAS/APO-1 promoter SNP with multiple sclerosis in the Altai region

I. Smagina
Altai State Medical University, Barnaul, Russian Federation

Background and aims: Violation of peripheral immune tolerance is involved in the pathogenesis of multiple sclerosis (MS). Binding of Fas/APO-1 receptors of autoreactive lymphocytes with Fas-ligand plays a critical role in the initiation of apoptosis. Object of study is to investigate the association of the SNP rs2234767 (1377G> A) in the promoter region of Fas/APO-1 gene with the MS.

Methods: 100 patients with relapsing-remitting MS, Russian, living in the Altai Region, and 100 volunteers without MS and other autoimmune diseases (control group) were participated in the study. Genotyping was performed by TaqMan allelic discrimination.

Results: The distribution of genotypes were not deviate from Hardy-Weinberg equilibrium (p=0.84; p=0.79, MS group and control respectively). We found significant associations between MS and genotype G/A (OR-1.74; 95% CI 1.07-2.82; p = 0.02), and the A allele (OR-2.94; 95% CI 1.25- 6.92; p = 0.01) of the SNP rs2234767 (1377G> A) of Fas/APO-1.

Conclusion: The findings suggest that the SNP rs2234767 (1377G> A) in the promoter region of Fas/APO-1 is associated with MS in the Altai region.

Disclosure: Nothing to disclose

Neuro-ophthalmology/-otology 1

P3175

Intravenous dexamethasone in acute management of vestibular neuritis: a randomized, placebo-controlled, single blind trial

I. Adamec[1], M. Krbot Skoric[1], T. Gabelic[1], B. Barun[1], J. Ljevak[2], A. Bujan Kovac[1], I. Jurjevic[3], M. Habek[3]
[1]Zagreb, Croatia, [2]Zagreb University Hospital Centre, Neurology, Zagreb, Croatia, [3]University Hospital Center Zagreb, Neurology, Zagreb, Croatia

Background and aims: Aim of this study was to evaluate the role of intravenous dexamethasone in relieving symptoms and signs of vestibular neuritis (VN) in the emergency department setting.

Methods: This was a randomized, placebo-controlled; single-blind study. Patients were randomized either to intravenous dexamethasone (group A) or placebo (group B) with all of the patients receiving symptomatic therapy. Primary outcome of the study was defined as necessity to hospitalize patients who present with VN in the emergency department. Secondary outcomes were: 1) improvement of nystagmus, 2) improvement of postural instability, 3) lessening of nausea, 4) lessening of vomiting, and 5) recovery of subjective symptoms.

Results: Altogether 100 patients were randomized, 51 into group A and 49 into group B. There was no difference in hospitalizations between groups (p=0.284). In both groups there was a statistically significant difference in values of all measured variables two hours after therapy intervention compared to baseline. In group A significantly less patients had 3rd degree nystagmus two hours after therapy intervention (p=0.000) while the difference in group B did not reach statistical significance (p=0.063). After therapy more patients had 1st degree nystagmus in group A (p=0.004) as well as in group B (p=0.0016) than before the intervention. There was a significantly greater absolute difference in European Evaluation of Vertigo scale results in group A when compared to group B (p=0.025).

Conclusion: Intravenous dexamethasone provides modest benefit in clinical recovery of VN. There is evidence of efficacy of antihistamines and benzodiazepines as symptomatic therapy in VN.

Disclosure: Nothing to disclose

P3176

Clinical recovery after acute vestibular neuritis

S. Cousins, D. Kaski, N. Cutfield, H. Ahmad, Q. Arshad, B. Seemungal, J. Golding, M. Gresty, A. Bronstein
Imperial College, London, United Kingdom

Background and aims: Clinical recovery after acute vestibular neuritis (VN) is variable and many patients report chronic symptoms. Symptoms correlate poorly with traditional vestibular-ocular reflex assessments. Accordingly, we prospectively assessed perceptual visuo-vestibular function and clinical outcome in patients presenting with acute vestibular neuritis.

Methods: 40 vestibular neuritis patients were studied in the acute (median 2 days), short (median 10 weeks; n=32) and long (>6 months; n=26) term recovery stages. Vestibular-ocular (VO) and vestibular-perceptual (VP) responses were measured at threshold and supra-threshold (90deg/s velocity step rotations) levels. Measures of visual dependency (Rod-and-disk test), clinical recovery (Dizziness Handicap Inventory) and psychological factors (HADS, BSQ and VSS-autonomic arousal) were obtained at each stage.

Results: Acutely, VO and VP vestibular thresholds were asymmetrically raised. Vestibular-ocular supra-threshold responses were asymmetric and reduced. However, VP supra-threshold responses were symmetrically reduced. There was no significant change in clinical recovery (DHI) after the short term recovery stage. Acutely increased visual dependency (p=0.006), autonomic anxiety (p=0.002) and fear of bodily sensations (p=0.05) predicted poor symptomatic recovery. Factor Analysis with DHI at short term recovery stage as dependent variable, showed a strong association between clinical recovery, visual dependency and psychological variables (HADS, VSS-AA and BSQ), all loading on a single component (49.21% of variance).

Conclusion: Vestibular-perceptual mechanisms exist that serve to suppress vertiginous sensations acutely, shown currently in the bilateral suppression of supra-threshold vestibular perception. Rather than being dependent on recovery of peripheral vestibular function, clinical outcome from acute VN is mediated by centrally modulated sensory integration mechanisms and psychological processing.

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P3177

White matter abnormalities in dizzy patients: retrospective cohort multi – centre study

H. Ahmad[1], N. Cerchiai[2], M. Mancuso[3], A.P. Casani[2], A. Bronstein[1]

[1]Imperial College London, London, United Kingdom, [2]Department of Medical and Surgical Pathology, Otorhinolaryngology Unit, Pisa University Hospital, Pisa, Italy, [3] University of Pisa, Neurological Clinic, Pisa, Italy

Background and aims: Although cerebral small vessel disease is a significant contributor to the development of imbalance and falls in the elderly, whether it also contributes to the development of dizziness is not known.

Methods: A retrospective case analysis was conducted for 125 dizzy patients referred to two neuro-otology tertiary centres in London and Pisa. Specific search criteria of "white matter disease" was applied to patient databases. Case notes were reviewed by a neuro-otologist and patients were divided into 'explained' causes of dizziness (ie benign vertigo ,orthostatic hypotension, cerebellar ataxias) and 'unexplained' causes of dizziness. Brain imaging was reviewed by a neurologist in conjunction with the neuroradiologist report. WM hyperintensities in MRI (T2 weighted and FLAIR) were rated according to the Fazekas scale.

Results: There were 61 patients (mean age=72,SD=7.95) in the 'unexplained' group and 64 (mean age=72.01, SD=8.28) in the 'explained' group. The overall frequency of lesions (Fazekas 1-3) differed between the unexplained and explained dizziness groups (p=0.015). The frequency of severe lesions (Fazekas 3) was significantly higher in the unexplained group (21%) than in the explained group (5%); chi squared test, p=0.005. Gait and postural abnormalities were more frequent in the unexplained group (44%) as compared to the explained group (25%).

Conclusion: The increased severity of WM abnormalities in cases of unexplained dizziness suggests that such abnormalities are contributory to the development of the dizziness. We postulate that WM lesions may induce dizziness either because patients perceive a degree of objective unsteadiness or by a cortical-subcortical disconnection syndrome.

Disclosure: This work was supported by the Medical Research Council of the U.K.

P3178

Central paroxysmal positional nystagmus: characteristics and possible mechanisms

J.-Y. Choi[1], M.H. Song[2], J.H. Kim[3], H.J. Kim[4], S. Glasauer[5], J.S. Kim[6]

[1]Ansan-si, Gyeonggi-do KP, Korea, Republic of, [2]SM Christiainity Hospital, Neurology, Pohang, Korea, Republic of, [3]Korea University College of Medicine, Neurology, Seoul, Korea, Republic of, [4]Kyungdong University, Goseong, Korea, Republic of, [5]University of Munich, Center for Sensorimotor Research, Munich, Germany, [6]Seoul National University Bundang Hospital, Seoul, Korea, Republic of

Background and aims: The diagnosis of central paroxysmal positional nystagmus (CPPN) is still challenging, and the mechanisms require further elucidation. This study aimed to determine the characteristics and mechanisms of CPPN.

Methods: 17 patients with CPPN were subjected to analyses of their clinical findings, MRI lesions, and oculographic data on spontaneous and positional nystagmus.

Results: The direction of CPPN was mostly aligned with that of the head motion during the positioning, and three types of CPPN were identified: downbeat nystagmus on straight-head hanging, upbeat nystagmus on up-righting, and apogeotropic nystagmus during supine head roll test. The direction of CPPN was aligned with the vector sum of the rotational axes of the semicircular canals that were normally inhibited during the positioning. The intensity of evoked nystagmus was at its peak initially and then decreased exponentially over time. The time constants (TC) of the vertical CPPN ranged from 3 to 8 seconds, which corresponds to the TC of the vertical rotational vestibulo-ocular reflex. Sixteen patients (94.1%) showed more than one type of CPPN. Furthermore, persistent downbeat or apogeotropic positional nystagmus was associated in 11 patients (64.7%). Most patients with CPPN from a circumscribed brain lesion showed an involvement of the cerebellar nodulus or uvula.

Conclusion: CPPN may be ascribed to enhanced responses of the vestibular afferents due to lesions involving the nodulus and uvula. CPPN could be differentiated from benign paroxysmal positional nystagmus by positional nystagmus induced in multiple planes, temporal patterns of nystagmus intensity, and associated neurological findings suggestive of central pathologies.

Disclosure: Dr. J.-S. Kim serves as an Associate Editor of Frontiers in Neuro-otology and on the editorial boards of the Journal of Clinical Neurology, Frontiers in Neuro-ophthalmology, the Journal of Neuro-ophthalmology, the Journal of Vestibular Research, and the Journal of Neurology; in addition, he received research support from SK Chemicals, Co. Ltd.; Dr. S. Glasauer receives research support from the German Research Foundation and the German Federal Ministry of Education and Research and has served as a reviewer for the European Commission. He is a shareholder of EyeSeeTec GmbH.; Others report no disclosures.

P3179

Retinal involvement in fronto-temporal dementia: role of optical coherence tomography and clinical implications

L. Ferrari, E. Coppi, F. Vitali, G. Magnani, G. Comi, L. Leocani

San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy

Background and aims: Frontotemporal dementia (FTD) is a clinical syndrome subtending a neurodegenerative process that involves mainly frontal and temporal lobes. Optical coherence tomography (OCT) is a non-invasive imaging technology that provides high-resolution cross-sectional images of retinal nerve fiber layer (RNFL).

Retinal neurodegeneration has been recently identified as a disease-phenotype in carriers of progranulin mutations before clinical onset of dementia.

The aim of our study was to investigate RNFL thickness in FTD patients compared to healthy controls (HC), also considering clinical and neuropsychological aspects.

Methods: 10 FTD patients (5 F, mean age 65+7 years) and 49 HC (26 F, mean age 68+7 years) underwent RNFL examination by spectral domain OCT. The two groups were compared through T-test, then a Pearson test was done to explore correlation between RNFL and age at OCT examination, disease duration, mini-mental state examination, proteins total-tau, phosphorylated-tau and amyloid-beta I-42.

Results: RNFL was significantly reduced as for global, superior and inferior quadrant, in patients compared to HC ($p= 0.05$): average 89.60+4.95 mm vs 98.37+7.46 mm; superior 111.20+10.62 mm vs 121.06+11.55 mm; inferior 112.40+9.93 mm vs 125.22+12.35 mm. RNFL thickness of FTD patients inversely correlated with disease duration. No significant correlations appeared between RNFL thickness and clinical-neuropsychological data.

Conclusion: Our data confirm the hypothesis of RNFL involvement in FTD. Future studies on larger samples will be needed to further explore neuropsychological and biomarkers correlations and to define the value of OCT as a rapid and high reproducible tool to monitor FTD evolution.

Disclosure: Nothing to disclose

P3180

Vestibulo-ocular reflex (VOR) deficit in spinocerebellar ataxia type 3: a possible disease biomarker?

C. Gordon[1], A. Zivotofsky[2], A. Caspi[3]

[1]Kfar-Saba, Israel, [2]Bar Ilan University, Brain Science, Ramat Gan, Israel, [3]Sami Shamoon College, Engineering, Ashdod, Israel

Background and aims: Spinocerebellar Ataxia Type 3 (SCA-3) is an autosomal dominant neurodegenerative disorder for which genetic testing can reveal those at risk for developing the disease. Quantitative measures that would identify pre-symptomatic gene carriers at the threshold of clinical diagnosis would be extremely valuable in early diagnosis, tracking disease progression, and assessing the efficacy of new treatments. Our objective was to investigate if eye movements can be used as biomarkers to quantify the appearance and progress of the disease even pre-symptomatically.

Methods: Using the magnetic search coil technique we recorded saccades, smooth pursuit, and VOR of 10 symptomatic SCA-3 patients and 4 subjects at risk for developing SCA-3. 3 of at risk subjects were genetically tested and found to have expanded "CAG" repeats in the ATXN3 gene. The fourth is a sibling of a symptomatic MJD patient who has declined genetic testing.

Results: 4 at risk subjects have a reduction in the gain of the VOR as measured using the head impulse test. Nonetheless, we did not find any deficit in either their saccades or smooth pursuit. In contrast, all of the symptomatic patients had saccadic and smooth pursuit deficits, in addition to impaired VOR. There was a trend of a negative correlation between VOR gain of the symptomatic patients and their ataxia score.

Conclusion: Individuals at risk for developing SCA-3 can be asymptomatic for years before receiving formal clinical diagnosis. Our preliminary results suggest that the VOR changes may serve as a biomarker of the disease.

Disclosure: Nothing to disclose

P3181

Glucorcorticoids improve dizziness symptoms following acute vestibular neuronitis

A. Batuecas-Caletrio[1], R. Yañez[1], C. Sanchez[2], S. Santa Cruz Ruiz[2], E. Gonzalez[2], L. Guardado Sanchez[2], D. Kaski[3]

[1]Universidad de Salamanca, Salamanca, Spain, [2]Hospital clinico universitario de Salamanca, Salamanca, Spain, [3]Imperial College London, London, United Kingdom

Background and aims: Vestibular neuronitis (VN) is characterized by acute vertigo, nausea, and imbalance without neurological deficits or auditory symptomatology. The symptoms of VN gradually improve over time as a result of a process of vestibular compensation in a majority of patients, but a significant proportion go on to develop chronic dizziness. The aim of this study was to explore the effect of glucocorticoid treatment on the degree of canal paresis in patients with acute VN, and critically, to establish its relationship with dizziness symptom recovery.

Methods and Materials: We recruited consecutive patients with VN who were assigned to one of two groups according to whether they received steroid treatment (n=32) or not (n=44). All patients underwent pure-tone audiometry, bithermal caloric testing, MRI brain imaging, and were asked to complete a dizziness handicap inventory at baseline and just prior to hospital discharge.

Results: In the steroid group, canal paresis was significantly lower than the control group (mean±SD %: 38.04±21.57 versus 82.79±21.51, $p<0.001$). Similarly, patients treated with steroids acutely had less severe nystagmus upon leaving hospital ($p=0.03$). Subjective dizziness scores were significantly lower in the steroid group at discharge (mean±SD %: 23.15±12.40 versus 64.07±12.87, $p<0.001$).

Conclusion: Patients who received steroid treatment showed greater symptomatic improvement, reduced hospital stay, and reduced canal paresis, than those treated conservatively. The results suggest that steroids may facilitate central vestibular compensation and thus reduce long-term morbidity.

Disclosure: Nothing to disclose

P3182

Head jolting nystagmus: head-shaking-induced occlusion of the horizontal semicircular canal

A. Bronstein[1], D. Kaski[1], N. Cutfield[2], D. Buckwell[1], R. Banga[3], J. Ray[4], S. Chavda[3], R. Irving[3]

[1]Imperial College London, London, United Kingdom, [2]University of Otago, Otago, New Zealand, [3]University Hospital Birmingham, Birmingham, United Kingdom, [4]Sheffield Teaching Hospitals, Sheffield, United Kingdom

Background and aims: We report a new syndrome (head jolting nystagmus, HJN) that expands the differential diagnosis of head-movement induced paroxysmal vertigo.

Case Report: Two male patients (65 and 58yrs).

Results: The patients described rotational vertigo after violent and brief (1-2s) oscillations of the head (head jolting) that triggered intense horizontal nystagmus lasting 45s. Accelerations of the head required to induce these episodes could only be achieved by the patients themselves. In Patient 1 the episodes gradually disappeared over a 6-year period. In Patient 2, 3-Tesla MRI suggested a filling defect in the left horizontal semicircular canal. He underwent surgical canal plugging that resolved the symptoms.

Conclusion: We attribute HJN to dislodged material within the horizontal semicircular canal, and provide a mechanistic model to explain its origin.

Disclosure: Nothing to disclose

P3183

Abstract cancelled

Peripheral nerve disorders 2

P3184

Cryoglobulinaemic neuropathy and peripheral neurotoxicity of interferon-alpha treatment: a retrospective study.

I. Allegri[1], L. Manneschi[2], L. Sacchelli[3], E. Montanari[2], G. Pavesi[4], F. Gemignani[4]

[1]A.O. di Parma, U.O. Neurologia, Parma, Italy, [2]AUSL Parma, U.O. Neurologia, Fidenza (PR), Italy, [3]A.O. di Parma, U.O. Malattie Infettive, Parma, Italy, [4]Università di Parma, Istituto di Scienze Neurologiche, Parma, Italy

Background and aims: Neuropathy related to interferon-alpha (IFNa) treatment for hepatitis C virus (HCV) infection has been occasionally reported, mainly in patients with mixed cryoglobulinaemia, as new onset neuropathy or as worsening of pre-existing (cryoglobulinaemic) neuropathy.

Methods: Retrospectively, we evaluated patients affected by cryoglobulinaemic neuropathy, examined at our Neuromuscular Service during the period 1998-2013, who underwent treatment with IFNa.

Results: Among 29 patients affected by cryoglobulinaemic neuropathy treated with IFNa, possible neurotoxicity was observed in 10 patients (9 women). Apparently, in 6 cases a painful neuropathy developed during the treatment. 4 patients had multiple mononeuropathy with sensorimotor involvement: in two patients a relapse occurred during treatment several years after neuropathy onset, whereas in two patients multiple mononeuropathy appeared during the last months of therapy with pegylated IFNa and ribavirin. In the remaining 19 patients neuropathy was unchanged or slightly improved after IFNa therapy.

Conclusion: The reported patients had either distal polyneuropathy or multiple mononeuropathy, variously related to IFNa treatment as triggering or exacerbating factor. Likely, clinical heterogeneity reflects different underlying mechanism, such as direct IFNa neurotoxicity or vasa nervorum damage mediated by modification of cryocrit and circulating immune complexes. Although our retrospective study did not consent epidemiological conclusions, it is intriguing that worsening or new onset of neuropathy occurred in about one third of patients with HCV-related cryoglobulinemia treated with IFNa. Potentials or actual IFNa neurotoxicity should be considere in patients with HCV infection, particularly if associated with cryoglobulinaemia, evaluating the opportunity to utilize, in alternative, newer antiviral therapies.

Disclosure: Nothing to disclose

P3185

Doppler ultrasonography findings in carpal tunnel syndrome: comparison of ultrasonographic findings with electrophysiological severity

N. Kutlar[1], A.O. Bayrak[1], I.K. Bayrak[2], S. Canbaz[3], H. Turker[1]

[1]Ondokuz mayıs university, Neurology, Samsun, Turkey, [2]Ondokuz mayıs university, Radiology, Samsun, Turkey, [3]Ondokuz mayıs university, Public Health, Samsun, Turkey

Background and aims: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. The diagnosis is based on history, clinical findings, physical examination and electrophysiological studies. Imaging techniques are reserved for cases that are difficult to diagnose and also informative about the morphology of the median nerve. More recently, it has been shown that Doppler ultrasonography can detect increased intraneural blood flow in CTS. The aim of our study is to evaluate the relationship between the severity of CTS and hypervascularization and cross sectional area (CSA); and to determine the diagnostic value of Doppler ultrasonography for CTS.

Methods: The patient group consisted of 125 wrists of 75 patients who were diagnosed with CTS, both clinically and electrophysiologically. The control group consisted of 100 wrists of 50 healthy volunteers. The hands were classified into five stages according to the electrophysiologic studies. A radiologist examined the groups blindly with gray scale and doppler ultrasonography and evaluated CSA and hypervascularization.

Results: A total of 121 wrists were included in the study. The CTS stage was found to be minimal in 28 hands, mild in 36 hands, moderate in 36 hands, and severe in 21 hands. The sensitivity and specifity of CSA and hypervascularization in detecting CTS was 90.9, 94.0, 93.4 and 90.0 % respectively. There was a significant correlation between severity of CTS and hypervascularization ($p < 0.05$) for all stages of CTS.

Conclusion: Our study suggests that the severity of CTS significantly correlates with Doppler sonography findings and this method is a useful complementary tool in identifying CTS patients.

Disclosure: Nothing to disclose

P3186

Recurring brachial neuralgic amyotrophy and facial dysmorphism

S. Beltran[1], B. De Toffol[1], A.-M. Guennoc[1], J. Laulan[2], P. Latour[3], P. Corcia[1]

[1]CHRU Bretonneau, Neurology, Tours, France, [2]CHRU Trousseau, Orthopedic & traumatic surgery, Tours, France, [3]Laboratory of medical biology, multisite of Lyon, Neurobiology, Bron, France

Background and aims: The hereditary neuralgic amyotrophy is difficult to diagnose because of its clinical heterogeneity. We report a case linked to a SEPT9 gene mutation.

Case Report: A patient of 16 years consulted for a sharp pain in the left arm occurring 10 days after a trauma and followed three weeks later by significant difficulties in using his arm. Clinically, there was a motor impairment of the entire left arm. The amyotrophy dominated in the proximal part. The deep tendon reflexes were abolished. The Electroneuromyography (EMG) examination pointed to a bilateral brachial plexopathy that dominated in the territories of radial and circumflex nerves (and median for motor impairment). There were also signs of chronic denervation and reinnervation. The cervical spinal MRI was normal. The existence of a similar episode at the age of 4 years in the right arm, without a triggering event, associated with an hypotelorism, led to evoke an hereditary brachial plexopathy linked to the mutation of SEPT9 gene. This diagnosis was confirmed by molecular biology that showed the p.R88W mutation.

Results: The recurring forms of brachial plexopathies are associated to 2 genes and 2 loci. The types related to the deletion of PMP-22 are associated with distal demyelination. The forms linked to SEPT9 are associated with facial dysmorphism that need to be searched for because of its association with mutation p.R88W.

Conclusion: The co-existence of painful, recurring and amyotrophying attack of the brachial plexus with an hypotelorism should lead systematically to seek the SEPT9 mutation.

Disclosure: Nothing to disclose

P3187

Relation between blood pressure profiles and functional status of Guillain-Barré syndrome

H.S. Lee, H.E. Lee, H.Y. Shin, S.M. Kim

Severance hospital, neurology, Seoul, Korea, Republic of

Background and aims: Autonomic dysregulation is not uncommon in Guillain-Barré syndrome (GBS). There is a paucity of information about the relation of blood pressure (BP) profiles and functional status of GBS patients. We aimed to study labile BP profiles in the early phase of GBS are correlated with poor functional status of plateau phase in GBS.

Methods: From January 2013 to August 2014, 37 patients with GBS were included. We analyzed BP profiles during initial 7 days as follows: mean BP, maximum BP, maximum BP – minimum BP, standard deviation (SD) of systolic blood pressure (SBP), and coefficient of variation (CV) of SBP, and that of diastolic blood pressure (DBP) and heart rate (HR). We serially checked GBS functional status by GBS disability score at base line, 1 week and 1 month from admission. The group with poor status was defined who has GBS disability score as high as 4, which corresponds with the inability to walk.

Results: 14 of 37 were poor status and this group had a significantly higher maximum, maximum-minimum, SD, CV of SBP and HR. The analysis by tertile categorization of SBP, HR parameters showed a dose-response relationship between most of the BP parameters and functional poor status.

Characteristics	Good state (n=23)	Poor state (n=14)	p value
Onset age (years)	51.7 ± 18.4	52.7 ± 18.7	0.883
Female, n (%)	5 (21.7)	7 (50.0)	0.146
Diarrhea, n (%)	3 (13.0)	7 (50.0)	0.023
URI, n (%)	10 (43.5)	5 (35.7)	0.641
Onset to admission (days)	7.7 ± 7.5	5.0 ± 7.4	0.290
MRC sum score at admission	2.2 ± 0.7	3.4 ± 1.0	< 0.001
Cranial nerve involvement, n (%)	14 (60.9)	8 (57.1)	0.823
GBS subtype			0.017
AIDP, n (%)	14 (60.9)	8 (57.1)	
AMAN, n (%)	0 (0)	4 (28.6)	
MFS, n (%)	9 (39.1)	2 (14.3)	
Anti-ganglioside Ab (+), n (%)	5 (21.7)	6 (42.9)	0.268
CSF study			
WBC (/μL)	3.13 ± 6.78	1.57 ± 2.02	0.410
Protein (mg/dL)	54.19 ± 41.45	58.30 ± 48.93	0.786
Onset to first EDx (days)	9.2 ± 7.6	5.5 ± 7.6	0.167
BP profiles, mm Hg			
SBP mean	134.7 ± 14.2	142.3 ± 13.5	0.120
DBP mean	80.2 ± 9.1	85.3 ± 10.1	0.124
HR mean	73.2 ± 9.8	87.1 ± 13.0	0.001
Treatment			0.032
No treatment	2 (8.7)	0 (0)	
IVIg, n (%)	20 (87.0)	9 (64.3)	
PLEX, n (%)	1 (4.3)	5 (35.7)	
Onset to last follow-up (days)	121.0 ± 129.3	184.7 ± 91.5	0.117
GBS diability score at last follow-up	1.1 ± 0.8	1.9 ± 1.5	0.165
Erasmus GBS outcome score	2.9 ± 0.8	5.3 ± 0.8	< 0.001

Patients demographics

	Good state(n=23)	Poor state (n=14)	p value
SBP mean	134.7 ± 14.2	142.3 ± 13.5	0.120
SBP maximum	158.9 ± 23.0	181.1 ± 25.0	0.009
SBP maximum-minimum	45.1 ± 25.3	80.5 ± 36.9	0.001
SBP SD	10.5 ± 3.76	17.4 ± 4.53	< 0.001
SBP CV	7.8 ± 2.65	12.3 ± 3.50	< 0.001
DBP mean	80.2 ± 9.19	85.3 ± 10.1	0.124
DBP maximum	100.6 ± 17.1	107.7 ± 11.4	0.185
DBP maximum-minimum	37.7 ± 16.7	46.4 ± 14.6	0.117
DBP SD	8.8 ± 2.79	10.5 ± 2.20	0.059
DBP CV	11.0 ± 3.63	12.4 ± 2.78	0.241
HR mean	73.2 ± 9.89	87.1 ± 13.0	< 0.001
HR maximum	89.5 ± 16.0	117.7 ± 27.8	< 0.001
HR maximum-minimum	28.2 ± 13.6	54.5 ± 27.4	< 0.001
HR SD	7.2 ± 3.21	12.7 ± 4.65	< 0.001
HR CV	9.9 ± 4.05	14.4 ± 3.79	0.002

Correlations between blood pressure parameters and functional status of GBS

Conclusion: Autonomic dysfunction occurs in approximately two-thirds of patients. Although it is still matter of a debate on relationship between autonomic dysregulation and functional status of GBS patients, this study highlight that variability of SBP and HR in the early phase of GBS is associated with functional status during plateau phase in GBS patients.

Disclosure: Nothing to disclose

P3188

Leflunomide-induced painful neuropathy. Report of three cases with small fibre involvement

L. Manneschi[1], V. Pietrini[2], I. Allegri[3], D. Santilli[4], F. Gemignani[2], E. Montanari[1]

[1]AUSL Parma, U.O. Neurologia, Fidenza (PR), Italy, [2]Università di Parma, Istituto di Scienze Neurologiche, Parma, Italy, [3]A.O. di Parma, U.O. Neurologia, Parma, Italy, [4]A.O. di Parma, U.O. Reumatologia, Parma, Italy

Background and aims: Leflunomide is an immunosuppressive drug used in rheumatoid and psoriatic arthritis. Occurance of polyneuropathy, usually of sensorimotor axonal type, has been reported in association with leflunomide, ranging from 1 to 10% of treated patients.

Methods: Case reports of 3 patients with leflunomide-induced neuropathy with features of painful small fibre type.

Results: Three men, aged 55, 54 and 52 years, affected by seronegative rheumatoid arthritis (two patients) and psoriatic arthritis, manifested neuropathic pain, replacing previous symptoms of arthritic pain, during leflunomide treatment at months 14, 3 and 10, respectively. Pain was deemed neuropathic by a clinical judgement, based upon the distribution of pain symptoms and the quality of symptoms, and confirmed by a total score of at least 4/10 (the cut-off value for the diagnosis of neuropathic pain) in the DN4 questionnaire. Small fibre neuropathy was diagnosed in 2 patients according to clinical criteria only, i.e. presence of both symptoms and signs related to small fibre involvement, and in one patient by skin biopsy showing decreased intraepidermal nerve fibre density in a non-lenght dependent distribution. Nerve conduction studies were negative.

Conclusion: Small fibre neuropathy has not been previously reported in association with leflunomide, but most studies were based upon electroneurographic findings, which do not individuate small fibre involvement. The neurotoxic risk of leflunomide therapy could be underestimated, as symptoms related to arthritis can confound the clinical picture obscuring neuropathic manifestations. A focused clinical evaluation considering subtle sensory symptoms and signs, using pain instruments, should be appropiate to define the occurence of leflunomide neuropathy.

Disclosure: Nothing to disclose

P3189

Genetic epidemiology of Charcot-Marie-Tooth disease in Hungary.

G.M. Milley[1], A. Gal[1], B. Bereznai[1], E.T. Varga[1], P. Balicza[1], Z. Aranyi[2], J. Boczan[3], P.D. Dioszeghy[4], M.J. Molnár[1]

[1]Semmelweis University, Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary, [2]Semmelweis University, Department of Neurology, Budapest, Hungary, [3]Department of Neurology, Medical and Health Centre of the University of Debrecen, Debrecen, Hungary, [4]Andras Josa Hospital, Department of Neurology, Nyíregyháza, Hungary

Background and aims: Charcot-Marie-Tooth neuropathies (CMT) are clinically and genetically heterogeneous disorders and belong to the most common hereditary neuromuscular diseases. This study aims to estimate the mutational frequency of the most common CMT gene (PMP22 MPZ, MFN2, Connexin 32 and EGR2) mutations among 550 Hungarian CMT patients (249 female and 301 male, mean age: 40,56±16.98) and to detect two founder mutations (NDRG1-R148X, CCFDN-IVS6+389C>T) in 15 Roma patients (11 female and 4 male, mean age: 39.88±14.87).

Methods: We performed mutational screening with MLPA, real-time PCR, PCR-RFLP and Sanger sequencing.

Results: The quantitative analysis of the PMP22 gene found 120 duplications and 77 deletions. Pathogenic mutations were detected in the MPZ gene in 19, in the Cx32 gene in 14, in MFN2 gene 5, in EGR2 gene in 3 cases and in PMP22 gene in 1 cases. In Roma patients LOM type neuropathy was present in 8, CCFDN mutation was found in 4 cases. In 1 family PMP22 duplication and EGR2 mutation coexisted. The genetic background of neuropathy was clarified in 45.6% of the patients.

Conclusion: In our presentation we would like to emphasize that mutation analysis of clinically and electrophysiologically well-characterized neuropathic patients reveals the genetic aetiology in a relatively large percent of cases.

Disclosure: Nothing to disclose

P3190

Electrodiagnostic criteria for Guillain-Barré syndrome: a need for reappraisal?

D. Parisis, G. Papadopoulos, E. Koufou, D. Karakostas
AHEPA University Hospital, [2]nd Neurology Department, Thessaloniki, Greece

Background and aims: It has been suggested that serial electrophysiology is essential for the reliable differentiation between acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). However, Rayabally Y et al. recently proposed a modified set of neurophysiological criteria that could make accurate diagnosis possible with a single nerve conduction study. We aimed to further clarify the influence of this set of criteria on the classification of Guillain Barré syndrome (GBS) subtypes.

Methods: We retrospectively reviewed records of 37 consecutive patients with GBS from Thessaloniki, Greece, admitted to our Department between 2006 and 2013. Electrophysiology was analyzed using existing criteria (Hadden et al. Ann Neurol. 1998) as well as the above mentioned criteria based on Van den Bergh criteria for AIDP (Muscle Nerve 2004) and incorporating new knowledge on electrophysiology of axonal GBS. For that purpose, exclusive presence of conduction blocks or isolated F-wave absence in two nerves were indicative of axonopathy.

Results: With existing criteria, patients were classified as having AIDP (65%), or AMAN (19%), or equivocal forms (16%). With modified criteria, AIDP was diagnosed in 54% and AMAN in 46% of patients. We observed a similar shift from AIDP to axonal GBS with modified criteria as that reported from studies that used serial nerve conduction studies (Uncini A et al., JNNP 2010)(20.8%vs 18.5%; p=0.7).

Conclusion: These data further support the utility of these criteria in the diagnosis of GBS subtypes, whereas prospective studies are clearly needed to verify these findings.

Disclosure: Nothing to disclose

P3191

A semi-automated method to assess IENFD in human skin biopsies

S. Seger[1], M. Stritt[2], K. Doppler[3], C. Sommer[3], A. Panaite[4], T. Kuntzer[5], A. Steck[6], A. Pagenstecher[7], A. Stalder[1]
[1]Allschwil, Switzerland, [2]Actelion Pharmaceutical, Allschwil, Switzerland, [3]Würzburg, Germany, [4]CHUV, Neurology, Lausanne, Switzerland, [5]CHUV, neurology, Lausanne, Switzerland, [6]University Hospital Basel, Department of Neurology, Basel, Switzerland, [7]Universitat Marburg, Marburg, Germany

Background and aims: The density of Intra-Epidermal Nerve Fibers (IENF) in skin biopsies is increasingly used as support for the diagnosis of peripheral neuropathies. The number of IENF is counted manually under a microscope in most histopathology labs. Unless the images are digitized, there is no documentation, and the method has an inter-rater and inter-lab variability of about 25%. Our aim was to develop a standardized, reproducible and documented semi-automated quantification of IENF density.

Methods: We analyzed samples from 4 different University Centers (Neuropathology/Neurology Basel, Neuropathology Marburg, Neurology Würzburg, Neurology Lausanne) stained according to local protocols. Images were acquired through the Z-plane using a whole slide scanner. ORBIT image analysis software was used to create an analyzable image and develop a reliable algorithm for IENF detection.

Results: The obtained rebuilt images revealed well-contrasted nerves allowing a reliable detection of fibers crossing the basal membrane (automated part). The software presents these nerves for quality check (manual part). Compared to the conventional count performed by histo-pathologists (2 independent University Centers), the presented semi-automated method achieved a correlation coefficient of 0.99 and 0.96 (Spearman r-test), and an inter-facility variability of 19% and 23%, respectively. We found a better reproducibility for fluorescence-stained specimens.

Conclusion: The new semi-automated method has a high experimenter-independent reproducibility when based on fluorescent nerve detection. This method is easy to handle even by untrained users. The IENF counting is electronically well documented

Disclosure: Nothing to disclose

P3192

Abstract cancelled

Cerebrovascular diseases 6

P3201

Spontaneous intracerebral haemorrhages in the posterior fossa: characteristics, associated factors, short and long-term outcome

C. Rossi[1], D. Strbian[2], N. Samarasekera[3], Y. Béjot[4], R. Al-Shahi Salman[3], M. Giroud[4], T. Tatlisumak[2], C. Cordonnier[1]

[1]University of Lille, UDSL, Inserm U[1171], CHU Lille, Department of Neurology, Lille, France, [2]Helsinki University Central Hospital, Department of Neurology and Stroke unit , Helsinki, Finland, [3]University of Edinburgh,, Division of Clinical Neurosciences, Center for Clinical Brain Sciences,, Edinburgh, United Kingdom, [4]University Hospital of Dijon, Department of Neurology, Dijon, France

Aims: To compare brainstem and cerebellar intracerebral haemorrhages (ICH) regarding baseline characteristics and outcome.

Methods: We selected patients with exclusively posterior fossa ICH from a cohort of 2,005 spontaneous ICH cases [two hospital-based cohorts (Lille, France, n=562; Helsinki, Finland, n=928) and two community-based studies (Lothian, Scotland, n=137, Dijon, France, n=378)]. We performed bivariate and multivariable logistic regression to investigate demographic, clinical, and radiographic associations.

Results: Posterior fossa ICH was present in 208 [10%; 95% confidence interval (CI) 9 to 11] patients; 39% were located in the brainstem and 61% in the cerebellum. In multivariable analysis, patients with brainstem ICH were more likely to have an excessive alcohol consumption (OR 7.2, 95%CI 2.5 to 21.4) and less likely to be treated with antihypertensive medications (OR=0.2; 95%CI 0.07 to 0.66). In-hospital case fatality rate was 43%, and was associated with the National Institute of Health Stroke Scale (NIHSS) score at presentation (OR 1.2; 95%CI 1.2 to 1.2), brainstem vs. cerebellar location (OR 19.8; 95%CI 2.0 to 193.2) and ICH volume (OR 1.1, 95%CI 1.0 to 1.2 per 1 ml increase). During one year of follow-up, no recurrent ICH occurred and survival did not differ between brainstem and cerebellar ICH.

Conclusion: Brainstem ICH differed from cerebellar ICH regarding risk factors and early outcome, but not longer-term outcome.

Disclosure: Nothing to disclose

P3202

Intervention versus aggressive medical management in carotid artery atherosclerosis: experience from a University Hospital in Hyderabad, India

K. Subhash, S. Alladi, S. Deepika, G. Sandeep

Nizam's Institute of Medical Sciences, Hyderabad, India

Background and aims: Based on the current guidelines, interventional (surgical or endovascular) revascularization of carotid artery stenosis is considered superior to medical therapy for secondary prevention of stroke. However, these guidelines are based on the studies done before the era of aggressive medical management. To investigate whether interventional (surgical or endovascular) revascularization is superior to the aggressive medical management.

Methods: Patients of ischemic stroke and transient ischemic attacks due to significant carotid artery stenosis (>50%) were given the option of medical or interventional treatment in the first 3 months following the stroke. Patients were followed up at 3 months, 6 months and 1 year after stroke.

Results: Out of 53 symptomatic patients, 40 preferred medical management and 13 opted for interventional management. Among these, 7 patients presented with TIA (13.3%) and 46 patients (86.7%) with stroke. The most common presenting symptom was left hemiplegia in 20 (37.7%) followed by right hemiplegia in 15 (28.3%) patients. Retinal symptoms were noted in 4 (7.5%) patients. Recurrence within one year was noted in 5 patients (12.5%) in medical management group and 2 (15.4%) patients of interventional group. One patient with recurrence in medical group and one patient with recurrence in surgical group had poor compliance to drugs.

Conclusion: There was no statistically significant difference in recurrence rate in medically or surgically managed group upto one year.

Disclosure: Nothing to disclose

P3203

New ultrasound ischemic leukoaraiosis indices, increased carotid artery stiffness and characteristics of cerebral hemodynamics in patients with ischemic leukoaraiosis

M. Turk[1], M. Zaletel[2], M. Zupan[2], J. Pretnar-Oblak[1], J. Kobal[3], B. Zvan[2]

[1]University Medical Centre Ljubljana, Department of Vascular Neurology and Intensive Neurological Therapy, Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Department of Vascular Neurology and Intensive Neurological Therapy, Ljubljana, Slovenia, [3]University Medical Centre Ljubljana, Department of Vascular Neurology and Intensive Neurological Therapy,, Ljubljana, Slovenia

Background and aims: The pathophysiology of ischemic leukoaraiosis (ILA) is unknown, but there are growing studies about increased arterial stiffness and changed hemodynamic parametersof intra and extracranial arteries in ILA patients. However, the diagnosis so far is still based on head MRI and exclusion of other causes appearing radiologically similar. Therefore we aimed to find vascular reliable markers of ILA using non-invasive widely available colour-coded duplex ultrasound and Trans Cerebral Doppler sonography (TCD).

Methods: We compared local carotid stiffness parameters and different hemodynamic parameters in the middle cerebral artery (MCA) in 53 LA patients to 40 gender and risk factor matched controls with normal MRI of the head. The ILA diagnosis was based on head MRI and the exclusion of other causes of white matter hyperintensities. We introduced new ILA indices (ILAi) that are ration of carotid stiffness parameters and MCA mean blood flow velocity. The associations between ILAi and ILA and diagnostic significance of ILAi for the prediction of ILA were analysed by SPSS 20.0

Results: We found significantly higher values of pulse wave velocity beta (PWVb, m/s), pressure-strain elasticity modulus (Ep, kPa) and beta index and lower diastolic, systolic and mean MCA blood flow velocities in the ILA group ($p \leq 0.05$). All ILAi significantly differed between the groups ($p<0.05$) and were significantly associated with ILA ($p<0.01$) The ROC curves showed that ILAi are sensitive and specific for predicting ILA ($p<0.05$).

Conclusion: New ILA indices are significant predictors of ILA and they have potentially diagnostic value in ILA patients.

Disclosure: Nothing to disclose

P3204

Assessment and frequency of cerebral microbleeds in the VMCI -Tuscany Study* cohort

R. Valenti[1], A. Del Bene[1], A. Poggesi[1], A. Ginestroni[1], E. Salvadori[2], G. Pracucci[2], S. Marini[1], S. Nannucci[1], M. Pasi[1], F. Pescini[1], M. Mascalchi[1], S. Diciotti[3], G. Orlandi[4], M. Cosottini[5], A. Chiti[4], U. Bonucelli[4], D. Inzitari[1], L. Pantoni[1]

[1]Florence, Italy, [2]University of Florence, Department of Neurological and Psychiatric Sciences, Florence, Italy, [3]Universtiy of Bologna, Department of Electrical, Electronic and Information Engineering „Guglielmo Marconi", Cesena, Italy, [4]University of Pisa, Department of Neurosciences, Pisa, Italy, [5]Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy, Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy

Background and aims: Cerebral microbleeds (MBs) are one of the neuroimaging expressions of small vessel disease. The aims of our study were to assess the reliability and feasibility of the Microbleed Anatomical Rating Scale (MARS) and describe presence and location of MBs in a cohort of patients with mild cognitive impairment (MCI) and leukoencephalopathy.

Methods: The VMCI Tuscany Study is a multicenter, observational study investigating predictors of transition from vascular MCI to dementia. MARS was used to assess the presence, number, and location of MBs. Detection of MBs was performed by consensus by 3 blinded raters. 20 MRI scans were independently reassessed by the three raters to evaluate inter-rater agreement (Landis and Koch, weighted kappa).

Results: MRI T2*-weighted gradient-echo sequences were available for 152 patients. Inter-rater agreement ranged good-very good (weighted kappa: 0.76-1.00). 41 patients (27%) had at least 1 MB (mean number: 3.7±4.8; range 1-18. MBs were located in infratentorial regions in 44% of patients, in deep regions in 51%, and in lobar regions in 56%. Analyzing the possible relationship between MBs and other expressions of SVD, the presence of lacunar infarcts was associated with higher number of total MBs ($p=0.008$), particularly with those in infratentorial and deep locations ($p=0.003$ and $p=0.045$, respectively).

Conclusion: The MARS scale proved to be a reliable and feasible instrument for the assessment of MBs. Inter-rater agreement was good to very good. Nearly one third of our patients had at least one MBs, and these were associated with the presence of lacunar infarcts.

Disclosure: Nothing to disclose

P3205

Uric acid in acute ischemic stroke: the URICIS study

S. Vidale[1], G. Carbotta[2], R. Condurso[3], A. Consoli[4], F. Galati[5], P. Postorino[5], M. Arnaboldi[1], S. Ricci[3], D. Consoli[5]
[1]Sant'Anna Hospital, Como, Italy, [2]La Sapienza University, Rome, Italy, [3]USL[1] Umbria, Città di Castello, Italy, [4]University of Florence, Florence, Italy, [5]Jazzolino Hospital, Vibo Valentia, Italy

Background and aims: Uric acid is a potent antioxidant agent. However, its role in the etiology and clinical outcome after an acute ischemic stroke is still unclear and debatable. Aim of this study was to evaluate the role of uric acid in a group of ischemic stroke patients.

Methods: Consecutive patients admitted to two Italian stroke units between 2012 and 2013 have been studied. Demographical data, vascular risk factors, admission and follow-up clinical features have been registered. Uric acid, creatinine, glomerular filtration rate (GFR), blood urea nitrogen and glucose have been tested for each patient. Statistical analysis was performed using chi-square and t-test for univariate analysis. A conditional logistic regression was applied to determine the significant prognostic negative factors.

Results: A total of 1,132 patients have been enrolled. Median age was 73 years and males were prevalent (602 cases). High blood pressure was the principal vascular risk factor (69%). Mean uric acid value was 5.9±4.2mg/dL and hyperuricemia was present in 404 patients. Hyperuricemia was associated to age, blood urea nitrogen and GFR ($p>0.001$). Hyperuricemic patients were mostly male and hypertensive ($p<0.05$).

Conclusion: Hyperuricemia was present mostly in elderly, hypertensive and altered renal function ischemic stroke patients.

Disclosure: Nothing to disclose

P3206

Cortical venous thrombosis due to intracranial hypotension after an epidural anesthesia

E. Viedma-Guiard[1], L. Crespo Araico[1], P. Agüero Rabes[1], C. Estévez Fraga[1], A. De Felipe Mimbrera[2], C. Matute Lozano[1], A. Alonso Cánovas[1]
[1]Hospital Ramón y Cajal, Neurology, Madrid, Spain, [2]Hospital Universitario Ramón y Cajal, Neurology, Madrid, Spain

Background and aims: Isolated cortical venous thrombosis is an infrequent subtype of cerebral venous thrombosis. Although large sinuses thrombosis may occurr in intracranial hypotension, isolated cortical venous thrombosis are extremely rare in this clinical condition.

Results: A previously healthy 20-year-old woman, in her fourth postpartum week, was admitted because of new onset persistent headache. Epidural anesthesia (wet tap) was performed before the delivery. Since then, she referred a daily pulsatile holocraneal orthostatic headache (with increased intensity when upright and decreased intensity when lying down). In addition, she had had several short episodes of right sided hypoesthesia during the week before admission. Neurologic examination, including funduscopy, was normal and meningeal signs were negative. Contrast-enhanced CT scan was normal while MRI scan showed a cortical venous thrombosis on the left parietal convexity, without abnormalities in parenchyma or large venous sinuses. Signs of decreased intracranial pressure were noticed, with descended cerebellar tonsils and generalised dural hyperintensity after gadolinium administration. Hypercoagulability screening tests were negative and extensive ancillary tests did not show any evidence of systemic disease.

Result: Clinical improvement with complete remission was achieved with conservative management (hydration and recumbent position resting).

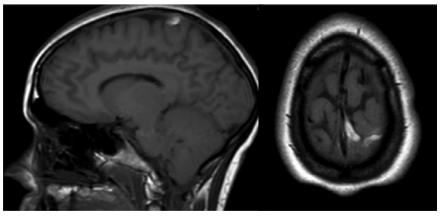


Fig. 1. MRI: Isolated cortical venous thrombosis in the left parietal convexity

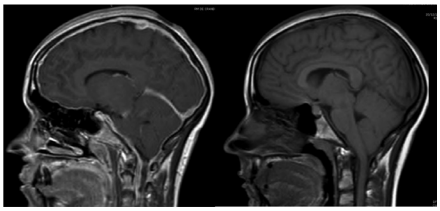


Fig- 2. MRI: a. Meningeal enhancement after gadolinium administration. b. Cerebellar tonsils descent.

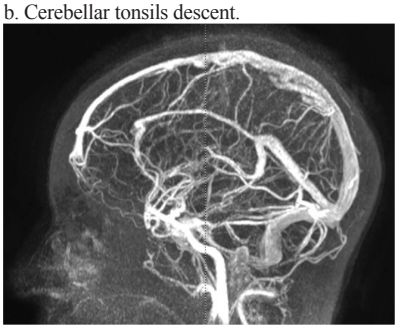


Fig. 3. MRI: Reconstruction of central nervous system venous sinuses.

Conclusion: We present an unusual case of cortical venous thrombosis due to cerebrospinal fluid hypotension in the prothrombotic context of puerperium. Wet epidural punctures should be closely monitored because of the risk of developing such complications, as our case illustrates.

Disclosure: Nothing to disclose

P3207

Etiological and clinical features of hemorrhagic stroke in young adults in northeastern China

L. Yin, Q. Fu, C. Ma

2nd Hospital of Dalian Medical University, Department of Neurology, Dalian, China

Background and aims: To investigate etiological and clinical features of hemorrhagic stroke in young adults in northeastern China.

Methods: 415 hemorrhagic stroke in young adults were collected which were admitted to our single center over the past 14 years. All cases were verified by imaging examinations. 201 cases received DSA. A retrospective analysis method was used.

Results: Of 415 cases, 263 were intracerebral hemorrhage and 152 subarachnoid hemorrhage (SAH). 313 cases had the onset in winter and spring while 102 cases in summer and autumn. Bleeding location include subarachnoid space in 152 cases, basal ganglion in 84 cases, cerebral lobes in 59 cases, thalamus in 45 cases, cerebellum in 29 cases, brainstem in 14 cases, multiple sites in 27 cases and others in 5 cases. DSA demonstrated brain arteriovenous malformation (AVM) in 76 cases, intracranial aneurysm (ICN) in 59 cases, Moyamoya disease (MMD) in 19 cases, dural arteriovenous fistula (DAVF) in 3 cases and cerebral venous thrombosis (CVT) in 2 cases. DSA was normal in the remaining 42 cases. 330 cases had a definite cause including essential hypertension, cerebral AVM, ICN, blood system diseases, MMD, perimesencephalic non-aneurysmal SAH, cavernous hemangioma, tumor stroke, puerperal stroke, DAVF, CVT, and connective tissue disease that were seen in 99, 76, 59, 28, 19, 15, 13, 11, 4, 3, 2 and 1 cases, respectively. However, the etiology in 85 cases (20.48%) was unknown .

Conclusion: Hemorrhagic stroke in young adults is becoming more common in northeastern China. Essential hypertension is the first cause followed by cerebral AVMs and ICNs. The etiology is unclear in around one-fifth cases.

Disclosure: Nothing to disclose

P3208

Ischaemic stroke in young adults: prospective study of 336 patients

I. Zinchenko[1], V. Lauer[1], O. Rouyer[1], V. Quenardelle[1], C. Marescaux[1], B. Geny[2], V. Wolff[1]

[1]Hôpitaux Universitaires de Strasbourg, Unité Neurovasculaire, Service de Neurologie, Strasbourg, France, [2]Hôpitaux Universitaires de Strasbourg, Service de Physiologie et des Explorations Fonctionnelles, Strasbourg, France

Background and aims: Few studies have comprehensively assessed the characteristics of ischaemic stroke (IS) in young adults.

Methods: We have prospectively studied a hospital-based series of 336 young adults (<45 years) between 2005 and 2014 with an acute IS confirmed by MRI. The patients were investigated by a standardized protocol including biological and toxicological screenings, cardiac and vascular check up.

Results: Mean age was 36.8±5.5, and the sex ratio was 1.2. As to the modifiable risk factors: tobacco use 48.5%, cannabis use 16.3%, and alcohol consumption 14.5%; potentially modifiable risk factors: dyslipidemia 41.3%, migraine 23.5%, oral contraceptive use for women 21.7%, hypertension 15.7%, history of stroke 5.9%, atrial fibrillation and diabetes less than 5% each. 8 women out of 149 were pregnant having stroke. Aetiologies by frequency were the following: cardioembolism 27%, intracranial arterial stenosis 18%, cervical dissection 12.2%, isolated patent foramen ovale 6%, haematologic in 4%, small vessel disease and aneurysm less than 1% for each. In 23.5% the aetiology remained undetermined. Clinical outcome was favourable with a mean discharge NIH scale score of 2.0±2.1. At 3 months, the mRS was inferior to 2 for 77% of patients.

Conclusion: We provide a description of the risk factors, aetiologies, clinical outcome characteristics of IS in a prospective series of young patients. The distribution of aetiologies among these young adults is different from those in the elderly which could be explained by the higher prevalence of lifestyle risk factors in this population.

Disclosure: Nothing to disclose

P3209

Safety of pre-operative aggressive antiplatelet treatment in patients with symptomatic carotid artery stenosis treated with early carotid endarterectomy.

C. Zompola[1], A. Roussopoulou[2], G. Georgioadis[3], M. Chondrogianni[2], C. Liantinioti[4], G. Papadimitropoulos[2], G. Dervenoulas[5], A. Lazaris[6], A. Tavernarakis[2], K. Vadikolias[7], M. Lazarides[3], S. Vasdekis[8], G. Tsivgoulis[7]
[1]Vrilissia - Athens, Greece, [2]Athens, Greece, [3]Department of Vascular Surgery, Democritus University of Thrace, School of Medicine, Alexandroupolis, Greece, Alexandroupolis, Greece, [4]LOUTRAKI CORINTHIAS, Greece, [5]Chaidari-Athens, Greece, [6]Department of Vascular Surgery, "Attikon" Hospital, University of Athens, School of Medicine, Athens, Greece, Alexandroupolis, Greece, [7]Alexandroupoli, Greece, [8]Department of Vascular Surgery, "Attikon" Hospital, University of Athens, School of Medicine, Athens, Greece, Athens, Greece

Background and aims: The association of pre-operative double antiplatelet therapy with neck haematoma (NH) complicating early carotid endarterectomy (CEA) in patients with symptomatic carotid artery stenosis (sCAS). Conversely, aggressive antiplatetel therapy (AAT) has been shown to decrease both asymptomatic microembolization and recurrent cerebrovascular events during the first days of ictus. The aim of this prospective, multicenter study was to evaluate the safety of pre-operative AAT in patients with sCAS treated with early CEA.

Methods: Consecutive patients with non-disabling acute ischemic stroke (AIS) or Transient Ischemic Attack (TIA) due to sCAS (≥70%) were treated with clopidogrel load (300mg) at hospital admission followed by the combination of clopidogrel (75mg) and aspirin (100mg) for 1 month. All patients underwent early CEA during the first two weeks of ictus. Bleeding complications and recurrent strokes during the first 30 days following stroke onset were prospectively recorded.

Results: A total of 97 patients with sCAS [mean age 67±9 years; 79% men; 58% AIS] underwent early CEA (median elapsed time from stroke onset to CEA 6 days, interquartile range 4-9). The only bleeding complications that were documented were 6 cases of NH (6.2%, 95%CI: 2.6%-13.1%). Re-exploration of the neck wound was required in two patients, while blood transfusions were administered in one. The rate of recurrent stroke prior to CEA was low (2.1%, 95%CI: 0%-7.7%). Recurrent strokes occurred during the hyperacute stroke stage (≤12 hours) in all cases.

Conclusion: Our findings underscore the safety profile of pre-operative AAT in patients with sCAS who are treated with early CEA.

Disclosure: Nothing to disclose

Cognitive neurology/ neuropsychology 3

P3210

Validation of the cube test - a cognitive screening tool - preliminary data

R. Barreto[1], L. Ruano[1], R.T Cruz[2], J. Pais[3], V.T. Cruz[1]
[1]CHEDV, Neurology, Feira, Portugal, [2]Utopia, Projectos de Arquitectura, Porto, Portugal, [3]Santa Maria da Feira, Portugal

Background and aims: The cube test consists of assembling six identical four sided indented pieces to reproduce that geometric form in the shortest period of time. The task relies on visuo-constructive, executive and processing speed abilities, frequently impaired in the initial forms of the most prevalent degenerative disorders. We report the initial validation of this cognitive test and relation with scores of other cognitive screening tests.

Methods: The test was applied in a large population-based cohort (EpiPorto) living in Oporto, Portugal. Time-to-first vertex, time-to-cube completion and number of correctly assembled pieces were recorded. Mini Mental state Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were also performed.

Results: We evaluated 845 individuals (mean age 62.8 years old; mean education 10.2 years, sd 5.6). The task was completed correctly by 86% of the participants. Mean time-to-first vertex was 45 seconds (sd 42.8s) and the mean time-to-cube completion was 97.6 seconds (sd 70.2s). Completion of task, time-to-first vertex and time-to-cube completion were significantly associated ($p<0.001$) with age, education level, MMSE and MoCA scores. Individuals with MoCA scores below age/education adjusted cutoffs for the Portuguese population were 15.6s slower to complete the cube than individuals performing above cutoffs ($p<0.05$).

Conclusion: The cube test showed good usability in a population-based cohort and the test parameters were significantly associated with validated cognitive assessment scales. Further test development and validation will be pursued in clinical studies to assess its feasibility as a screening tool for the most prevalent neurodegenerative diseases.

Disclosure: Nothing to disclose

P3211

Stigma of Alzheimer's disease: what do professionals perceive?

L. Cartz Piver[1], B. Calvet[1], N. Dumoitier[2], J.P. Clement[1], P. Couratier[1]
[1]University Memory Clinic, Limoges, France, [2]University of Medicin, Limoges, France

Background and aims: Alzheimer's disease (AD) is a progressive neurological disorder leading to memory and cognitive decline and disability. Stigma against AD contributes to the burden of patients and families, and adds to the strain of professionals involved in the management of the disease.

Methods: Professionals of the COGLIM memory network of Limousin (France) filled out the STIG-MA questionnaire anonymously. The STIG-MA questionnaire is 10 questions from the EMIC (Explanatory Model Interview Catalogue, 1992): each is scored from 0 (signifying the least stigma) to 3 (signifying the most stigma). The sum of all the questions is the STIG-MA score.

Results: 243 professionals completed the STIG-MA questionnaire. 75% were women, the average age was 48. They were general practicioners (GP) (14%), pharmacists (PH) (13%), nurses (NU) (31%), psychologists (PS) (10%) and others (32%). The global STIG-MA score was 9.9 (±4.8): the lowest stigma was expressed by the PS (8.5). Emotional impact (loss of self-esteem, shame) was strongly expressed by all the professionals, but less by GPs. Working in a retirement home or training in gerontology-geriatrics did not influence stigma. Professionals aged over 50 expressed more stigma.

Conclusion: This study shows differences in stigma of professionals who care for AD patients. The main factor that seems to influence stigma is age. Further studies are necessary to address this issue and to define strategies to help professionals in their work.

Disclosure: Nothing to disclose

P3212

The effects of age-related brain changes on mental state attribution using the standardized version of the story-based empathy task

A. Dodich[1], C. Cerami[2], N. Canessa[3], C. Crespi[1], G. Lettieri[1], S. Iannaccone[4], A. Marcone[4], A. Falini[5], D. Perani[1], S. Cappa[3]
[1]Vita-Salute San Raffaele University, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neurosciences, Milan, Italy, [3]San Raffaele Scientific Institute, Milan, Italy, [4]San Raffaele Hospital, Milan, Italy, [5]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: Normal aging is characterized by progressive brain volumetric reduction, mainly involving prefrontal, temporal and parietal regions. Since mentalizing partially relies on the same regions involved in age-related neurodegeneration, these observations suggest that a decline in the ability to understand other minds may reflect concomitant grey matter (GM) changes associated with aging.
Methods: To test this hypothesis we evaluated the effect of aging on mentalizing abilities in 34 middle-aged and elderly subjects (age range 43-76 years), who underwent a voxel-based morphometry (VBM) magnetic resonance imaging study and performed a task (i.e., the story-based empathy task) assessing the ability to infer others' intentions and emotions.
Results: VBM provided evidence of an age-related GM volume reduction in the frontal lobe, including the inferior frontal gyrus (IFG), and in temporal regions (hippocampus, temporal pole (TP) and superior/middle temporal gyrus). Moreover, while global performance was positively related to GM volume in the precuneus, GM volume in the left IFG, right superior/middle temporal gyrus and bilateral TP positively correlated with mentalizing performance based on affective cues.
Conclusion: The study shows an association between age-related brain shrinkage in frontal and temporal structures and mentalizing, measured through the standardized version of a simple, non-verbal task assessing both intention and emotion attribution skills.
Disclosure: This work has been partially supported by the MIUR grant "I meccanismi neurocognitivi alla base delle interazioni sociali" (PRIN2010XPMFW4_008), and by the Università degli Studi di Milano-Bicocca CARIPLO grant „Dottorato ad alta Formazione in Psicologia Sperimentale, Linguistica e Neuroscienze Cognitive". Dr. Cerami was funded by Fondazione Eli-Lilly (Eli-Lilly grant 2011 „Imaging of neuroinflammation and neurodegeneration in prodromal and presymptomatic Alzheimer's disease phases").

P3213

Patterns of impaired cognitive and affective Theory of Mind in bvFTD and AD patients

A. Dodich[1], C. Cerami[2], C. Crespi[1], G. Lettieri[1], N. Canessa[3], S. Iannaccone[4], A. Marcone[4], D. Perani[1], S. Cappa[3]
[1]Vita-Salute San Raffaele University, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neurosciences, Milan, Italy, [3]San Raffaele Scientific Institute, Milan, Italy, [4]San Raffaele Hospital, Milan, Italy

Background and aims: Theory of mind (ToM) can be differently impaired in course of neurodegeneration. In this study, we assessed affective and cognitive ToM in a sample of dementia (i.e. Alzheimer's disease (AD) and behavioral variant of frontotemporal dementia (bvFTD)) and predementia (i.e. amnestic mild cognitive impairment, aMCI) patients. The relationship between ToM sub-conditions and an executive control task condition was evaluated.
Methods: We enrolled 35 patients (i.e.,12 AD, 20 bvFTD and 15 aMCI fulfilling IWG criteria for AD in predementia phase) and 35 healthy controls (HC). Subjects performed the Story-based Empathy task (SET), a non-verbal task measuring the ability to infer others' intentions (IA) and emotions (EA) compared to a control condition (causal inferences, CI). Global and single sub-condition scores as well as the balance between the two ToM sub-conditions and the control condition were evaluated with a vectorial approach.
Results: While dementia patients showed impaired performances on all SET sub-conditions, aMCI presented no significant difference compared to HC. Additional analyses highlighted a specific impairment in the balance between EA and CI conditions in bvFTD.
Conclusion: Our study showed impaired intention and emotion attribution in AD and bvFTD with comparable global performances on the task. Nevertheless, the vectorial analysis supports a pure ToM deficit in the attribution of mental states based on affective cues in the bvFTD group. In contrast, the overall deficit in the task in AD appears to be related to the severity of dementia. This latter finding is further supported by the normal performance of the aMCI group.
Disclosure: This work has been partially supported by the MIUR grant "I meccanismi neurocognitivi alla base delle interazioni sociali" (PRIN2010XPMFW4_008), and by the Università degli Studi di Milano-Bicocca CARIPLO grant „Dottorato ad alta Formazione in Psicologia Sperimentale, Linguistica e Neuroscienze Cognitive". Dr. Cerami was funded by Fondazione Eli-Lilly (Eli-Lilly grant 2011 „Imaging of neuroinflammation and neurodegeneration in prodromal and presymptomatic Alzheimer's disease phases").

P3214

Near-death experiences in patients with locked-in syndrome (LIS): not always a blissful journey

V. Charland[1], Z. Lugo[1], J.-P. Jourdan[2], A.-F. Donneau[3], V. Blandin[4], F. Pellas[5], S. Laureys[1]

[1]Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Liege, Belgium, [2]International Association For Near Death Studies, Oraison, France, [3]University of Liège, Liège, Belgium, Department of Public Health, Liege, Belgium, [4]ALIS - Association du Locked-In Syndrome, Boulogne-Billancourt, France, [5]Médecine Rééducative, Hôpital Caremeau, CHU Nîmes, Nîmes and Association for Locked-in Syndrome (ALIS), Nîmes, France

Background and aims: We here aimed at retrospectively characterizing the content of NDEs in patients with LIS having suffered from an acute brainstem lesion (cerebrovascular accident (CVA) or trauma; i.e., "LIS NDEs") and to compare these experiences to those collected in a cohort of NDE experiencers after coma with supratentorial lesions (CVA or trauma; i.e., "classical NDEs").

Methods: Differences between groups were assessed using Student's t-test and a Pearson's chi square test or Fisher's exact test using SPSS (Chicago, IL, USA). Results were considered to be significant at the 5% critical level ($p<0.05$) and were expressed as mean ± standard deviation (SD) for quantitative variables and as counts and proportions (%) for categorical variables.

	"LIS NDEs" n=8 (%)	"classical NDEs" n=23 (%)	p value
Gender - female	5 (63)	12 (52)	0.890
Etiology	7 brainstem CVA (88) 1 brainstem trauma (12)	20 supratentorial CVA (87) 3 supratentorial trauma (13)	0.968
Age at NDE (Mean in years ±SD)	31 ± 6	31 ± 14	0.959
Time since NDE (Mean in years ±SD)	19 ± 9	19 ± 9	0.732

Table 1- Demographical information

Results: 14 patients with LIS recalled having had memories of their coma period. 8 (57%) qualified as a NDE according to the Greyson NDE scale criteria (i.e., total score ≥7). "LIS NDEs" reported less frequently feelings of peacefulness (96% vs. 38%, respectively, $p<0.001$) and joy (70% vs. 25%; $p=0.028$) and more frequently experienced life review during the NDE (26% vs. 75%; $p=0.032$).

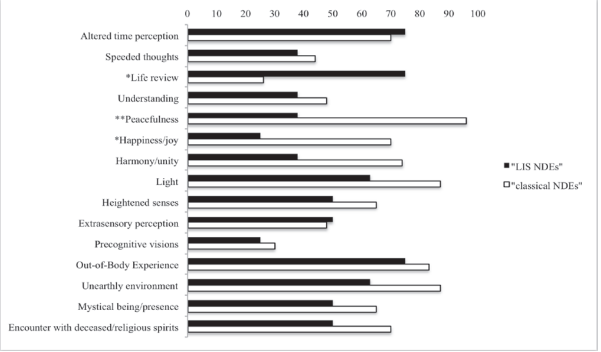


Figure 1- Comparison of reported features according to the Greyson NDE scale

Conclusion: Patients with LIS who retrospectively report an NDE subsequent to an acute brainstem lesion of ischemic or traumatic origin, experience this event as less positive as compared to "classical" NDEs following coma after supratentorial brain damage. Less positive NDEs might have a specific neuroanatomical substrate related to impaired pontine/paralimbic connectivity or alternatively might be related to the emotional distress caused by the presence of conscious awareness in a paralyzed body.

Disclosure: Nothing to disclose

P3215

Memory impairment in thalamic stroke patients: implication of the mamillo-thalamic tract

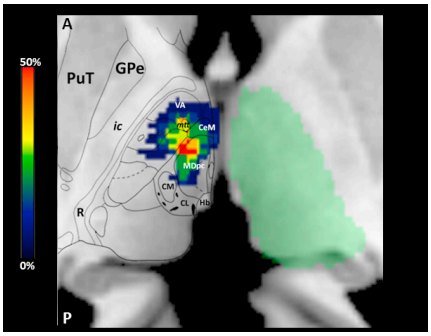
L. Danet[1], E. Barbeau[2], P. Eustache[3], N. Raposo[4], I. Sibon[5], J.-F. Albucher[6], F. Bonneville[7], P. Peran[8], J. Pariente[7]

[1]Inserm U825 - CerCo CNRS - CHU Purpan, Toulouse, France, [2]CerCo CNRS - CHU Purpan, Toulouse, France, [3]Inserm U825, Toulouse, France, [4]CHU Purpan, neurologie, toulouse, France, [5]CHU Pellegrin, Bordeaux, France, [6]CHU Purpan, Neurologie, Toulouse, France, [7]CHU Purpan - Inserm U825, Toulouse, France, [8]INSERM U825, neurologie, Toulouse, France

Background: Thalamic amnesia has been described but mechanisms underlying memory impairment remain equivocal. It is unclear if thalamic amnesia is directly related to damage of some specific nuclei or indirectly related to mamillothalamic tract (MTT) lesion. The present study aimed to better understand mechanisms of thalamic amnesia.

Methods: We assessed 12 subjects with a left thalamic infarction. They were matched for age and education level to 25 controls. Subjects underwent a neuropsychological assessment including verbal and visual memory, executive functions, language and behaviour. Participants received a volumetric MRI scan. Patients' lesions were manually segmented and localized within the thalamus using an innovative method. We then segregated the patient group in two subgroups: iMTT and dMTT (intact/damaged) according to damage of the MTT intact (iMTT) and damaged (dMTT). Cognitive performance was compared between patients and controls. We then compared cognitive performance between the two subgroups: iMTT and dMTT. Correlation between memory performance and MTT volume and mediodorsal volume loss were assessed.

Results: Most of the lesions were located in the mediodorsal and in the intralaminar nuclei. Six patients presented a lesion of the MTT. Patients performed worse than controls in verbal memory. Patients' performance was also lower in executive functions. iMTT group and dMTT group differ in verbal recall only. A significant correlation was found between recall and MTT volume in the patients' group. No correlation was found for mediodorsal volume loss.



Overlap of left thalamus lesions (% of patients, N=12) on axial view (upper, A: anterior, P: posterior). PuT: putamen, GPe: globus pallidus external, ic: internal capsule, R: reticular nucleus, VA: ventral-anterior, mtt: mamillothalamic tract, CeM: centra

Conclusion: This study shows that MTT damage play an important role in amnesia occurrence after a thalamic stroke.

Disclosure: Nothing to disclose

P3216

Diagnostic utility of the Clock Drawing Test and relationship with Alzheimer's disease CSF biomarkers

D. Duro[1], I. Baldeiras[2], R. Lemos[3], L. Letra[4], B. Santiago[5], I. Santana[6]

[1]Coimbra, Portugal, [2]Centro Hospitalar e Universitário de Coimbra, Laboratório de Neuroquímica, Coimbra, Portugal, [3]Faculty of Psychology, University of Coimbra, Coimbra, Portugal, [4]Centro Hospitalar e Universitário de Coimbra, Neurology Department, Coimbra, Portugal, [5]CHUC, Neurology, Coimbra, Portugal, [6]Centro Hospitalar e Universitário de Coimbra, Neurology, Coimbra, Portugal

Background and aims: Mild Cognitive Impairment (MCI) is a recognized entity representing patients with a significantly higher probability of developing Alzheimer's disease (AD). Several neuropsychological measures have been studied in trying to establish the best tool to predict progression to AD in individuals with MCI. The diagnostic utility of the Clock Drawing Test (CDT) has been studied rather extensively but its relationship with specific AD biomarkers remains unclear. We explored the relationship between common cognitive screening instruments, the CDT and AD CSF biomarkers in a sample of MCI subjects.

Methods: 81 MCI subjects were assessed with the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), the Alzheimer's Disease Assessment Scale (ADAS) and the CDT (Rouleau, Cahn and Babins scoring systems). CSF parameters analyzed included Aβ42, Tau, phosphorylated-tau and an index which classified MCI patients in MCI or MCI-due to AD (according to the 2011 McKhann criteria).

Results: 46 (56.8%) patients were classified as MCI-due to AD. We found significant moderate correlations between the all CSF parameters, except Aβ42, and the MMSE, and less significant correlations with the MoCA and ADAS. There was no correlation between the CDT and CSF biomarkers. The MCI-due to AD group had a significantly lower performance in all tests, but there were no differences in CDT scores between the two groups.

Conclusion: Our results support the higher adequacy of specific cognitive screening instruments for the detection of MCI patients at higher risk for developing AD, confirming the low utility of the CDT in milder forms of cognitive impairment where memory is the primary deficit.

Disclosure: Nothing to disclose

P3217

Modulation of GABAA receptor signaling increases neurogenesis and suppresses anxiety through NFATc4

M. Elnaggar[1], G. Quadrato[2], C. Duman[2]

[1]Tübingen, Germany, [2]Hertie institute for clinical brain research, Tübingen, Germany

Background and aims: Correlative evidence suggests that GABAergic signalling plays an important role in the regulation of activity-dependent hippocampal neurogenesis as well as of emotional behaviour in adult mice. However whether these are causally linked at the molecular level remains elusive. NFAT proteins are activity-dependent transcription factors that respond to environmental stimuli in different cells types, including hippocampal newborn neurons.

Methods: Here we identify NFATc4 as a key activity-dependent transcriptional regulator of GABA signalling in hippocampal progenitor cells via an unbiased high throughput genome wide study.

Results: Next, we demonstrate that GABAA receptor signalling modulates hippocampal neurogenesis through NFATc4 activity, which in turn regulates GABRA2 and GABRA4 subunit expression via binding to specific promoter responsive elements as assessed by ChIP and luciferase assays. Furthermore, we show that selective pharmacological enhancement of GABAA receptor activity promotes hippocampal neurogenesis via calcineurin/NFATc4 axis. Importantly, NFATc4 dependent increase in hippocampal neurogenesis following GABAA receptors stimulation is required for the suppression of the anxiety response in mice.

Conclusion: Taken together, these data provide a novel molecular insight into the regulation of the anxiety response in mice suggesting GABAAR/NFATc4 axis as a druggable target for the therapy of emotional disorders.

Disclosure: This research have been performed by grants from DFG and Fortune grant from the University of Tübingen.

Critical care

P3218

Continuous electrodermal activity in comatose survivors after a cardiac arrest: a potential new biomarker for prognosis?

V. Alvarez[1], C. Reinsberger[2], B. Scirica[3], M. O'Brien[3], K. Avery[4], G. Henderson[5], J. W. Lee[6]

[1]Sion, Switzerland, [2]Universität Paderborn, Sportmedizinisches Institut, Paderborn, Germany, [3]Brigham and Women's Hospital, Department of Cardiology, Boston, USA, [4]Brigham and Women's Hospital, Department of Nursing, Boston, USA, [5]Brigham and Women's Hospital, Department of Neurology, Boston, USA, [6]Brigham and Women's Hospital, Neurology, Boston, USA

Background and aims: Electroneurophysiology is important for prognostication after cardiac arrest (CA). While it is possible to identify accurately patients with bad outcomes, it is still difficult to predict who will recover. Autonomic dysfunction measured by electrodermal activity (EDA) may reflect the depth of coma and could represent a new biomarker. Continuous EDA recording through is investigated in this setting.

Methods: In this prospective study, EDA was recorded continuously, during therapeutic hypothermia and normothermia, in comatose adult patients after cardiac arrest. A novel wrist-worn skin conductance biosensor incliding two silver coated electrodes applied on the wirst was used. Association between EDA parameters and later signs of awakening from coma were assessed.

Results: 18 patients were enrolled. Recordings started at a median of 18.4 hours (range: 8 - 41) after CA and lasted 43.45 hours (0.3 – 68.3) (see example in Figure 1). All phasic EDA parameters, also know as "electrodermal responses" (EDR), during TH were associated with outcome. A higher number of EDR and higher median amplitudes were seen in patients with later awakening from coma (see Table 1 and Figure 2). The tonic parameter, or the base line, was similar in both groups.

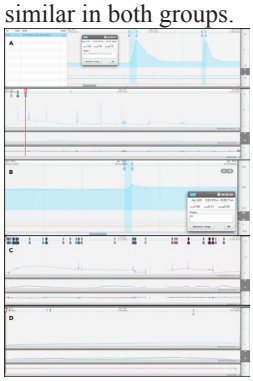


Figure 1: A: View of the complete display with the 24 hours record on the bottom and the "zoom" widow on the top right (2 min/page) showing two electrodermal responses during endotracheal tube aspiration and their measurement.

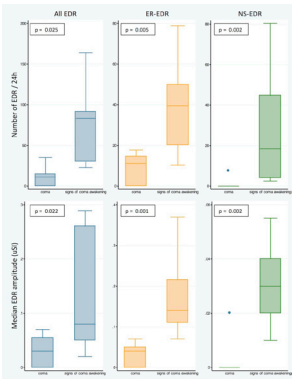


Figure 2: Comparison of patients who remained comatose with the ones with signs of awakening from coma using boxplots of EDA parameters during therapeutic hypothermia. The first line displays the number of electrodermal response / 24 hours and the second

	Electrophysiology during Hypothermia			Electrophysiology during Normothermia			
	Coma n=8	Signs of awakening from coma n=10	p	Coma n=8	Signs of awakening from coma n=10	p	
EEG							
Reactivity	0 (0%)	9(90%)	**<0.001**	0 (0%)	10 (100%)	**<0.001**	Fisher's exact
Background							
• Continuous	0(0%)	1 (10%)		0 (0%)	7 (70%)		
• Nearly continuous	0 (0%)	1 (10%)		0 (0%)	2 (20%)		
• Discontinuous	0 (0%)	3 (30%)		1 (14.3%)	1 (10%)		
• Burst-Suppression	4 (50%)	5 (50%)		5 (71.4%)	0 (0%)		
• Suppressed	4 (50%)	0 (0%)	**0.039**	1 (14.3%)	0 (%)	**0.005**	Fisher's exact
Myoclonus status epilepticus	4 (50%)	0 (0%)	**0.023**	4 (57.1%)	0 (0%)	**0.015**	Fisher's exact
EDA parameters (n=16)	**n=7**	**n=9**		**n=7**	**n=9**		
• SCL (uSi)	0.44 (0.05 – 1.63)	0.355 (0.06 – 1.04)	0.69	0.5 (0.09 – 1.62)	0.47 (0.27 – 1.09)	0.3	Wilcoxon rank sum
• Total number of EDR	11.2 (0 - 35.25)	83.4 (22.7 - 164)	**0.025**	20.8 (1 – 44.4)	50 (23.25 – 678)	**0.01**	Wilcoxon rank sum
• Median delta of all EDR (uSi)	0.03 (0 – 0.07)	0.08 (0.02 - 0.289)	**0.022**	0.12 (0.045 – 0.65)	0.11 (0.04 – 0.17)	0.5	Wilcoxon rank sum
• Total number of ER-EDR	11 (0 - 17.7)	39.5 (10.4 - 78.9)	**0.005**	19.2 (1 – 44.4)	24 (18.6 – 188)	0.12	Wilcoxon rank sum
• Median delta of ER-EDR (uSi)	0.04 (0 - 0.07)	0.14 (0.07 - 0.37)	**0.001**	0.14 (0.05 – 0.914)	0.18 (0.05 – 0.295)	1	Wilcoxon rank sum
• Total number of NS-EDR	0 (0 - 7.52)	18.4 (2.5 - 80.35)	**0.002**	0 (0 – 5.45)	19.7 (0 – 490)	**0.008**	Wilcoxon rank sum
• Median delta of NS-EDR (uSi)	0 (0 - 0.02)	0.03 (0.01 - 0.055)	**0.0019**	0 (0 – 0.03)	0.03 (_0 – 0.12)	**0.02**	Wilcoxon rank sum

Table 1: Comparison of patients that remained comatose and dose that showed signs of awakening from coma regarding electrophysiology (EEG and EDA) during hypothermia and normothermia

Conclusion: Continuous electrodermal recording may be a new neurophysiologic biomarker of awakening from coma after CA, with many EDA features being different between patients with signs of awakening from coma from and those remaining comatose. Because this technology is convenient to implement in the intensive care unit, it may open a new field in brain function monitoring in neuro-critically ill patients.

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P3219

Predictors of cognitive outcome in traumatic coma patients

N. Khizanishvili, M. Khaburzania, T. Kherkheulidze, M. Beridze
Tbilisi State Medical University, Neuromedicine, Tbilisi, Georgia

Background and aims: To investigate the possible predictors of cognitive outcome in patients recovered from traumatic coma.

Methods: Totally 75 traumatic coma patients investigated. Consciousness rated by Glasgow Coma Scale (GCS). Vegetative state (VS) and minimally conscious state (MCS) diagnosed according to international criteria. Coma recovered patients accessed by Disability Rating Scale (DRS). Cognitive status evaluated by Mini Mental Examination Scale (MMSE). Patterns of EEG background activity detected by 16 channel EEG. Brain conventional CT or MRI (1.5 T) was done in all patients. Auditory long latency evoked potentials (ALLEP) were studied by 16 channel EEG with regime for evoked potentials. Statistical analysis performed by SPSS 11.0.

Results: At one month 26 coma patients (GCS= 4-7) with alpha and delta EEG patterns died, 24 patients (GCS=5-8) with beta (33.4%), delta (25%) and theta (41.6%) coma developed VS. Among them14patients detected to have MCS and 11patients showed ALLEP (GCS=4-8) with theta EEG. Another 25 (GCS=5-8) patients with beta (28%), theta (54%) and delta (18%) background EEG recovered with different DRS (2-14) and MMSE (14-20). Positive correlation established between MCS patients with high amplitude frontal and temporal lobe theta frequencies and ALLEP (P-300) ($r=+0.47$; $p<0.01$). Logistic regression (entered stepwise model including patients' age, brain lesion size and site, EEG pattern, GCS, DRS) toward MMSE revealed the significance of high amplitude theta EEG ($p<0.00$) after adjustment with ALLEP (P-300).

Conclusion: The high amplitude theta background EEG with positive ALLEP is significant for favorable cognitive outcome in traumatic coma patients.

Disclosure: Nothing to disclose

P3220

Active and passive paradigms of consciousness in non-communicating patients: a meta-analysis

D. Kondziella
Copenhagen, Denmark

Background and aims: Active and passive paradigms based on functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG) may reveal consciousness in vegetative (VS) or minimal conscious states (MCS). Whereas active paradigms suggest a higher degree of certainty, passive paradigms may allow detecting signs of consciousness in patients who are unable to cooperate in cognitive tasks. A meta-analysis was performed in order to assess whether the clinical diagnosis is accurately reflected by signs of consciousness revealed by fMRI and EEG, including command following (active paradigms) and preserved cognitive event-related potentials and/or relevant cortical activation (passive paradigms).

Methods: Eligible studies were selected from multiple indexing databases through December 2014 and evaluated using standardized systemic review methods.

Results: 31 studies were identified, including data from 913 patients (mean age 43 years, range 16 to 89; male/female 2.1:1; 39.5% traumatic brain injuries). MCS patients were more likely than VS patients to follow commands during active paradigms (32% versus 15%; odds ratio 2.68 (95% CI 1.76-4.07; $p<0.0001$)) and to show preserved cortical connectivity during passive paradigms (68% versus 26%; odds ratio 5.9 (95% CI 4.0-8.66; $p<0.0001$)).

Conclusion: In non-communicating patients, active paradigms may underestimate the degree of consciousness as compared to passive paradigms. While MCS patients are more likely to show signs of preserved consciousness in both paradigms, a significant number of VS patients are able to follow commands by modifying their brain activity. However, there are important limitations at the single-subject level; for instance, patients from both categories may show command following although passive paradigms are negative.

Disclosure: Nothing to disclose

P3221

Predictive risk factors for delayed neurologic sequelae after carbon monoxide poisoning

H. Kuroda[1], K. Fujihara[2], S. Kushimoto[3], M. Aoki[1]
[1]Tohoku University Graduate School of Medicine, Department of Neurology, Sendai, Japan, [2]Tohoku University Graduate School of Medicine, Multiple Sclerosis Therapeutics, Sendai, Japan, [3]Tohoku University Graduate School of Medicine, Division of Emergency and Critical Care Medicine, Sendai, Japan

Background and aims: Delayed neurologic sequelae (DNS) is a relapse of neurologic deficits after carbon monoxide (CO) poisoning. Although several studies mentioned the risk factors associated with DNS, reliable predictive risk factors have not been established. We aimed to reveal predictive risk factors for DNS.

Methods: This study was designed as a prospective, observational study. We analysed clinical and laboratory data of patients experiencing acute CO poisoning. The patients were followed until 3 months after acute poisoning. We categorised patients showing a relapse of neurologic deficits as patients with DNS, and patients showing no deficits as patients without DNS.

Results: Of 93 patients experiencing acute CO poisoning [median, 46 years; 72% male], 16 patients (17%) developed DNS, and 77 (83%) did not. By univariate analyses, predictive risk factors for DNS were the lowest score of Glasgow Coma Scale <10, duration of CO exposure >6.25 hours, duration of consciousness disturbance >24.5 hours, globus pallidus lesion on brain CT, white blood cell count >11,900, CRP >0.15, CK >514, serum bilirubin index, defined as [(bilirubin at 24-48 hours after acute poisoning) / (bilirubin within 12 hours after acute poisoning)], <1.056. By logistic regression analyses, [odds ratio, 95% confident interval, P-value] were globus pallidus lesion [17.8, 2.13-238, 0.0069], CRP >0.15 [16.8, 2.32-347, 0.0039], and serum bilirubin index <1.056 [19.4, 3.24-173, 0.0009].

Conclusion: The knowledge about the predictive risk factors for DNS will be useful for risk stratification of patients experiencing acute CO poisoning.

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P3222

Air bubbles in the air: cerebral air embolism in commercial flights

B. Oyanguren[1], A. Alonso Cánovas[2], A. De Felipe Mimbrera[3], I. Hernández Medrano[3], V. Sánchez González[4], I. Prieto[5], J.C. Martinez Castrillo[3], J. Martínez San Millán[6], I. Corral Corral[3], J. Masjuan Vallejo[2], A. Escobar-Villalba[2]
[1]Hospital Universitario de Torrejón, Neurology, Madrid, Spain, [2]Hospital Ramón y Cajal, Neurology, Madrid, Spain, [3]Hospital Universitario Ramón y Cajal, Neurology, Madrid, Spain, [4]Hospital General Virgen de La Luz, Neurology, Cuenca, Spain, [5]Hospital Universitario Ramón y Cajal, Intensive Care Unit, Madrid, Spain, [6]Hospital Universitario Ramón y Cajal, Radiology, Madrid, Spain

Background and aims: Cerebral air embolism (CAE) may exceptionally occur in patients with thoracic lesions during air travelling. The risk for this complication and prognostic factors are unknown.

Methods: We present 3 new cases of CAE during commercial flights and a review of literature.

Results: 3 patients with CAE have been admitted to our Emergency Department: two males (B, C), one female (A). All experienced loss of consciousness (LOC) early in the course of a commercial flight with subsequent seizures. Chest radiograph showed thoracic bullae in all cases. Brain computed tomography (CT) scan showed subarachnoid bubbles in A, several intraparenchymal bubbles in B, and global hypoperfusion on multimodal CT in C. Magnetic resonance imaging was normal in A, showed bilateral infarctions and edema in B, and diffuse edema with posterior ischemic lesions in C. All received supportive treatment. A and C survived, B died. Including ours, 14 cases (7 female, mean age 55, 19-71) of CAE associated with commercial flights have been reported. LOC and dyspnea early in the flight were common. Thoracic cysts (7) and bullae (7) were found. 5 received hyperbaric oxygen therapy. 9 died, 2 remained moderate-severely disabled. In the 3 patients with complete recovery, infarction, edema and intraparenchymal bubbles were absent in basal neuroimaging. 5 patients had previously experienced neurological problems onboard.

Conclusion: CAE is an infrequent but serious complication of air travelling increasingly recognized. Neuroimaging findings may constitute a prognostic factor.
Thoracic cystic lesions bear a risk for CAE which has not been estimated.
Diagnosing non fatal CAE may help prevention.

Disclosure: Nothing to disclose

P3223

Comparison of interrater reliability and predictive validity of FOUR score and Glasgow Coma Scale in multi traumatic patients

F. Seifar[1], S. Shams Vahdati[2]
[1]*students research committee,Tabriz University of medical Sciences, Tabriz, Iran,* [2]*Tabriz, Iran*

Background and aims: Multi traumatic injuries impose health care concern and major burden for society. The Glasgow Coma Scale (GCS) is a routine scale for assessing levels of consciousness and prognosis of traumatic patients. The Full Outline of UnResponsiveness (FOUR) score is a new coma scale developed to overcome the limitations of GCS. In this prospective study we aimed to compare the predicting outcomes and inter-rater reliability of the GCS and FOUR score in a group of multi traumatic patients.

Methods: 96 consecutive muti traumatic patients admitted emergency department were enrolled in the study. GCS and FOUR score were documented on arrival to emergency room. Their correlation with patients 'outcomes was analysed. Inter-rater reliability was also assessed using κ score.

Results: In terms of predictive power for in-hospital mortality, calculated mortality rate was 33.1 for FOUR score and 30.21 for GCS. Mean value of GCS and FOUR score were 14.83 and 13.68, respectively. Mortality rate was determined 9.3% and mean duration of hospitalisation was 7.86±8.73 days. In addition, inter-rater reliability was determined κ=0.84±0.01 for GCS score and κ=0.86±0.01for FOUR score rating. Inter-rater reliability and outcome predictability for FOUR score was superior to the GCS in this study, therefore FOUR score can be considered as a viable alternative to the GCS in emergency department by accurately predicting outcome and improving the quality of management in traumatic patients.

Disclosure: Nothing to disclose

P3224

Moderate hypothermia after perinatal asphyxia and instrumental predictors of outcome (Saint Petersburg, Russian Federation)

M. Shumilina[1], A. Skoromets[2], V. Garaev[3], J. Gorelik[3], V. Lubimenko[4]
[1]*St. Petersburg Medical University J.P. Pavlow, Neurology department, Saint-Petersburg, Russian Federation,* [2]*North-West State Medical University n.a. I.I. Mechnikov, Saint-Petersburg, Russian Federation,* [3]*City Children's Hospital #1, NICU, Saint-Petersburg, Russian Federation,* [4]*City Children's Hospital #1, Saint-Petersburg, Russian Federation*

Background and aims: We have quantified usage of amplitude integrated electroencephalography (aEEG and neurosonography (NS) in newborns treated with moderate hypothermia (during 72 hours) after sever asphyxia for short-term outcome prediction in newborns.

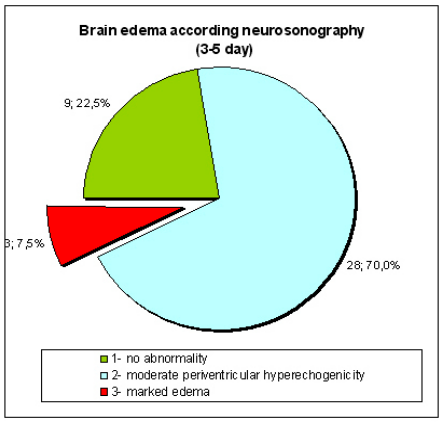
Methods: 40 term neonates with severe perinatal asphyxia were cooled in NICU of City Children's Hospital (Sept. 2011 – Oct. 2012). All children were monitored by one-channel aEEG: after arrival at NICU, 24-48 hours of life, 3-5 days of life (70% of newborns). NS was made for all patients on 3-5, 7-10 and 28 days of life. Outcomes was estimated on 28-30 d of life. Spearman rank correlation and line regression analysis were developed to assess NS and aEEG at 3-6 hours, 24 and 72 after asphyxia as predictors of short-term outcome.

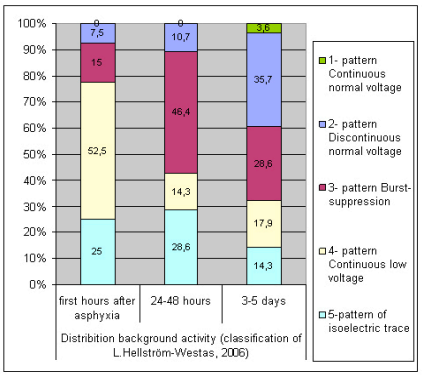
Results: Apgar score was 1 and 4 (median) at 1 and 5 minutes, respectively. Duration of mechanical ventilation was 10.1±1.8 days, length of hospital stay was 32.6±3.4 days. 10 patients (25%) by the end of the neonatal period had unfavorable outcome (death(5%)/ vegetative state/ forming spastic tetraparesis + somnolence). Correlation of severity of hypoxic-ischemic encephalopathy (HIE) and pattern of aEEG conducted at the age of 1 day ($p<0.0001$; $r=0.70$) and 3-5days ($p=0.01$; $r=0.52$) was found. For aEEG conducted on admission correlation with clinical severity is not revealed. The most predictive indicator for NS was the presence of ischemia of the basal ganglia(3-5days of life) ($p=0.03$; $r=0.40$).

Perinatal characteristics and short-term neonatal outcomes

Characteristics and short-term outcomes	n (%) / mean (±SE)/ median (IQR)
Maternal Baseline Characteristics (n=40)	
Mean maternal age, years (±SE)	29,5 ± 1,0
Primipara	30 (75)
Placental abruption	2 (5)
Emergency Caesarean section	5 (12,5)
Forceps / ventouse	4 (10)
Cord entanglement around the fetus	5 (12,5)
Meconium-stained liquor	5 (12,5)
HIV-positive	1 (2,5)
Infant baseline characteristics (n=40)	
Mean gestational age, weeks	39,5 ± 0,2
Birth weight, g	3531 ± 93
Birth length, cm	51,7 ± 0,4
Male gender	57,5 (23)
Median Apgar score (IQR):	
1 minute	1 (1-2)
5 minute	4 (3-4)
10 minute	5 (4-5)
Initial pH	7,09 ± 0,05
Initial BD, mmol/l	15,41 ± 1,33
Initial lactate, mmol/l	6,7 ± 0,9
Initial pCO2, mm Hg	50,81 ± 5,20
Initial glucosae, mmol/l	6,05 ± 0,6
Clinical seizures during 24 h after asphyxia	39 (97,5)
Stage of HIE (H.B.Sarnat и M.S.Sarnat):	
2 stage	3 (7,5)
3 stage	37 (92,5)
Mortality in the neonatal period	2 (5)
Duration of mechanical ventilation, days	10,1 ± 1,8
Beginning of enteral nutrition, day	5,2 ± 1,1
Length of hospital stay, days	32,6 ± 3,4

BD - Base Deficit; HIE - hypoxic-ischemic encephalopathy; h – hours.





Conclusion: Using NS (evaluating "status marmoratus") and aEEG after 24 hours of life can help to predict unfavorable outcome in the end of neonatal period of term newborns with HIE treated with hypothermia. Moderate hypothermia is safe and effective.

Disclosure: Nothing to disclose

P3225

The electroencephalogram as a predictor of somatosensory evoked potentials in patients with impaired consciousness

J. Vynckier[1], M. Schrooten[2]

[1]Scherpenheuvel, Belgium, [2]University Hospitals Leuven, Neurophysiology, Leuven, Belgium

Background: To identify a correlation between the pattern on electroencephalography (EEG) and the presence or absence of the N20 response on somatosensory evoked potentials (SEP) in coma patients.

Methods: We conducted a retrospective analysis to identify all patients who were admitted to an ICU and received both EEG and SEP for prognostic evaluation. EEGs were categorized according to Young's classification, SEPs were divided into three categories according to the presence or absence of the N20 response. Functional outcome at six months was categorized according to the Glasgow Outcome Scale. Primary outcome was the correlation between the EEG and SEP category. Secondary outcomes were correlation between the results of electrophysiological investigations and the functional outcome.

Results: We identified 2380 patients over a period of 16 years. For practical reasons, the 120 patients who were admitted in the last two years were the subject of our study. Overall mortality at six months was high in our population with 85%. Inter-rater variability for the EEG readings was excellent with a kappa value of 0.76. Correlation of EEG and SEP category was significant with rs of 0.519 ($P<0.001$). Negative predictive value for unilaterally as well as bilaterally absent N20 response was 100%.

Conclusion: For coma patients who receive predictive evaluation with both EEG and SEP, a strong correlation exists between the EEG pattern and the N20 response. The unilateral absence of an N20 response is almost as robust a predictor of poor functional outcome as bilaterally absent N20 responses.

Disclosure: Nothing to disclose

Epilepsy 3

P3226

A long-term experience of monotherapy in a tertiary epilepsy center: comparison between oxcarbazepine and levetiracetam

B.S. Kang, S.K. Lee
Seoul, Korea, Republic of

Background and aims: To evaluate and compare the long-term efficacy and safety of oxcarbazepine (OCB) and levetiracetam (LEV) based on a large population of patients at a tertiary epilepsy center.

Methods: All patients who were using OCB or LEV at the Seoul National University Hospital between January 2007 and March 2009 were recruited. Patients who had received brain surgery for seizure control or who had associated progressive disease were excluded from this study.

Results: A total of 307 patients were recruited. 158 of the 177 patients treated with OCB and 58 of the 130 patients treated with LEV had localization-related epilepsy (LRE). In the LRE subgroup, 86 patients (54.4%) with OCB and 36 patients (52.9%) with LEV remained seizure free during the follow-up period (P=0.837). LEV was also effective for juvenile myoclonic epilepsy (57.1% seizure-free rate) and epilepsy with generalized tonic–clonic seizure (62.5% seizure-free rate). The 3-year retention rates in patients treated with OCB and LEV were not significantly different (81.4% vs 72.1%; P=0.781). General weakness (11.9% vs 4.6%; P=0.027) and skin rash (4.0% vs 0%; P=0.022) were more frequent in the OCB group, whereas irritability (0.6% vs 33.8%; P<0.001) was more frequent in the LEV group.

Conclusion: OCB and LEV were effective and safe as a monotherapy for partial epilepsy. LEV was also effective for the treatment of generalized epilepsy.

Disclosure: Nothing to disclose

P3227

Ictal cardio-respiratory depression: a real risk for SUDEP?

E. Pasini[1], F. Provini[1], L. Volpi[2], R. Michelucci[2]
[1]*Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy, Bologna, Italy,* [2]*IRCCS of Neurological Sciences of Bologna, Bellaria Hospital, Bologna, Italy*

Background and aims: Cardio-respiratory dysfunctions during epileptic seizures have been extensively investigated during the last years as a possible risk factor for SUDEP (Sudden Unexpected Death in Epilepsy).

Here we report a 60-year-old woman affected by focal cryptogenetic left fronto-temporal lobe epilepsy associated with ictal asystole and central apnea.

Case Report: The patient underwent prolonged video-polygraphic (EEG-ECG-respiratory) monitoring in the telemetry unit because of a 58-year history of hypermotor nocturnal seizures preceded by epigastric discomfort and associated, in the last 25 years, with choking sensation.

Results: We recorded several sleep-related seizures arising from the left fronto-temporal regions complicated by asystole (max 12s) and prolonged central apnea (more than 30s). The patient was rapidly implanted with pace-maker (PM). Repeat post-implant monitoring demonstrated the persistence of ictal apnea concomitant to the activation of PM, in the absence of significant hypoventilation.

Conclusion: Our case highlights the possibility of huge cardio-respiratory dyscontrol during ictal discharges, which might be fatal in some patients. However the life-long history of dysautonomic ictal symptoms in our patient seems to challenge the usefulness of PM implant and assisted ventilation in such conditions.

Disclosure: Nothing to disclose

P3228

Two-year real-world experience of perampanel in elderly patients with refractory focal epilepsy

A. Rohracher, I. Deak, J. Dobesberger, J. Höfler, G. Kalss, G. Kuchukhidze, M. Leitinger, E. Trinka
Paracelsu Medical University Salzburg, Department of Neurology, Salzburg, Austria

Background and aims: Elderly adults >60 years have a high incidence of epilepsy and seizure recurrence. Choice of antiepileptic drug (AED) in this group is influenced by seizure type, tolerability and comorbidities. Real-life data were used to investigate treatment response and adverse events (AEs) with perampanel in the elderly versus a younger population.

Methods: Clinical registry data for elderly patients (>60 years) were compared with those <60 years from a cohort of 85 adults with focal onset epilepsy who have received perampanel since 09/2012. Treatment response and AEs are reported according to age group, while controlling for perampanel dose and concomitant anti-epileptic drugs (AEDs).

Results: 20 elderly patients (7 female; mean age 69.8 years, SD 11.5) and 65 younger patients (39 female; mean age 36.8 years; SD 11.5) were included. Over 57 months, 75% (15/20) elderly patients and 53.8% [35/65] younger patients were still taking perampanel. 35% (7/20) elderly patients were seizure free compared with 13.8% (9/65) younger patients (p=0.009). 35% (7/20) of elderly patients experienced AEs compared with 55.4% (36/65) younger patients (p=0.563). Speech effects (30%) and fatigue (20%) were the most common adverse effects in the elderly group, while vertigo (40%) and psychiatric effects (9.2%) were most common in younger patients.

Conclusion: Perampanel efficacy and tolerability in the elderly population mirrors that seen in younger patients. These real-life data suggest a broad patient base for whom perampanel may be a useful add-on treatment, potentially leading to improved safety, independence and quality of life in elderly patients.

Disclosure: A. Rohracher received travel support from EISAI.

P3229

Familial cerebral cavernomas: identification of a novel KRIT1 gene mutation

I. Rosário Marques, F. Antunes, N.E.T. Ferreira, M.D. Grunho
Almada, Portugal

Background: Cerebral cavernomas are vascular malformations that may occur in sporadic or familial forms. Familial forms have autosomal dominant inheritance, wherein three genes have been identified: KRIT1/CCM1, CCM2 and PDCD10/CCM3.

Case Report: A 31-year-old previously healthy female presented with a three years' duration epileptic disorder, with daily complex focal seizures characterized by altered consciousness, manual and oromandibular automatisms, and automatic speech. Subsequent brain MRI revealed numerous bilateral cortical cavernomas, and the EEG documented right temporal focal paroxysmal activity. Seizure control was achieved with antiepileptic duotherapy. The proband's 50-year-old mother was found to have a history of focal seizures initiated at age 13 and surgical excision of a cortical cavernoma at age 27, with a subsequent seizure- and medication-free period of 8 years. Seizures, characterized by disturbance of consciousness and right upper limb dystonic posturing, restarted at age 35 and fully remitted with carbamazepine. Brain MRI showed multiple encephalic cavernomas. The genetic testing for familial forms of cerebral cavernomas detected, in both patients, a heterozygous mutation in KRIT1 gene, consistent with the diagnosis of Hereditary Cerebral Cavernous Malformation type 1. This mutation, c.947_948insAC(p.Leu317Argfs*2)-exon10, is not yet described in the literature.

Conclusion: The pathogenic KRIT1 mutation identified in this family is not yet described in the literature. The careful and thorough follow-up of patients, and respective families, with multiple cerebral cavernomas is essential for the clinical, imaging and genetic characterization of this disease, particularly while trying to identify the factors that influence its treatment and prognosis.

Disclosure: Nothing to disclose

P3230

Inflammation and apoptotic markers in adult patients with epilepsy: is there any link?

A. Kegler[1], R.S. Scalco[2], C. Almeida[1], D. Santana[1], E.T. Pascotini[1], J. Arend[1], P. Gabbi[1], I.B. da Cruz[1], M.M. Duarte[1], L.F. Royes[1], M.R. Fighera[1]
[1]Universidade Federal de Santa Maria, Santa Maria, Brazil, [2]University College London, London, United Kingdom

Background and aims: Epilepsy in adult people is generally a chronic disorder frequently associated with a variety of factors. We aimed to investigate if there is a link between neuroinflammation, apoptotic markers and oxidative markers in epilepsy pathophysiology.

Methods: A cross-sectional study of 43 patients presenting with epilepsy and a control group of 41 healthy people was performed. Inflammatory markers, apoptotic markers and DNA damage were evaluated and included TNF-alpha (TNF-α), caspase-3 (CASP-3) and PicoGreen (PG). A correlation between inflammatory and apoptotic markers were analysed.

Results: Statistical analyses showed that patients with epilepsy presented higher levels of TNF-α ($p<0.001$) as compared to the control group. We observed that patients with epilepsy had significantly higher serum CASP-3 ($p<0.001$) and PG ($p<0.001$) than the control group. Statistical analysis revealed a significant correlation between inflammatory and apoptotic markers in the epilepsy group ($p<0.05$).

Conclusion: These findings suggest an important link between inflammatory and apoptotic markers and epilepsy in the studied sample.

Disclosure: Nothing to disclose

P3231

Prescribing for epilepsy in adult patients with an intellectual disability and/or pervasive developmental disorder: a systematic review

Z. Doran[1], R. Shankar[1], L.J. Sander[2], W. Lee[3], C. Dale[4], M. Kerr[5], L. Richard[6], B.N. McLean[7], J. Devapriam[8], K. Wilson[9], J. Craig[10], M.C. Walker[2], R. Hillier[11], D. Cox[9], M.J. Sadler[12], M. Mohan[13]
[1]Cornwall Partnership NHS Foundation Trust, Neuropsychiatry, Truro, United Kingdom, [2]London, [3]Plymouth University, Peninsula Schools of Medicine & Dentistry, Plymouth, United Kingdom, [4]Cornwall Partnership NHS Foundation Trust, Research, Truro, United Kingdom, [5]Cardiff University, Psychological Medicine and Clinical Neurosciences, Cardiff, United Kingdom, [6]Cornwall Partnership NHS Foundation Trust, Psychiatry, Truro, United Kingdom, [7]Truro, [8]Leicestershire Partnership NHS Trust, Acute & Low Secure Mental Health Services, Leicestershire, United Kingdom, [9]Cornwall Partnership NHS Foundation Trust, Truro, United Kingdom, [10]Belfast, [11]United Kingdom, [12]Plymouth, [13]North Bristol NHS Trust, Bristol, United Kingdom

Background and aims: About a quarter of people with epilepsy (PWE) have intellectual disability (ID) and/or Pervasive Developmental Disorders (PDD) such as autism. This group has higher mortality, significant communication issues, difficulties making informed choices and greater risks of chronic physical and mental health co-morbidities. There is no specific prescribing guidance for this cohort of PWE and ID. We aimed to systematically review the literature on Anti Epilepsy Drug (AED) prescribing in this group, in particular examining different needs of the ID population.

Methods: We undertook a literature review using the search engines PubMed/Medline, EMBASE, PsychINFO and Google-scholar to identify a current evidence base for AED prescribing in PWE and ID, PDD and associated genetic syndromes.

Results: The search strategy returned 224,817 results. Of these 45 were included for analysis. 17 were systematic reviews, 16 cohort studies, 6 randomised control trials and 4 case control studies. 224, 772 were excluded due to small sample size or irrelevance.

Conclusion: PWE and ID/PDD tend to have various mental health and physical health co-morbidities and as a result can respond differently to medications when compared with the general population. The review identified very few studies which looked systemically at the influence of AEDs in PWE and ID/PDD. In the last 15 years there is no major research looking at the influence of the newer AEDs in this vulnerable population. In addition to the lack of research, no structured method exists for safely and effectively examining the safety of new AEDs in populations with an ID/PDD.

Disclosure: Nothing to disclose

Movement disorders 8

P3234

Help-seeking for mood problems in people with Parkinson's disease: A qualitative analysis

A. Simpson[1], M. Samuel[2], R. Brown[1]
[1]King's College London, Institute of Psychiatry, Psychology & Neuroscience, Psychology, London, United Kingdom, [2]East Kent University Hospitals NHS Foundation Trust/King's College Hospital, Neurology, Ashford/London, United Kingdom

Background and aims: Mood problems in Parkinson's disease (PD) are often as, if not more, disabling than motor symptoms and can affect between approximately 30-50% of patients. However, patients with these problems often do not receive effective treatment. Reasons for this include: patients not reporting such problems, and issues surrounding illness beliefs and treatment preferences. Help-seeking, or actively seeking help for a problem, is influenced by these factors. Currently, there is little understanding of the help-seeking behaviour of people with Parkinson's (PwP) for mood problems. The objective of this study is to understand the factors associated with help-seeking for mood problems in PwP, from the patient and carer perspective.

Methods: In-depth qualitative interviews were conducted with 10 PwP and 10 carers of PwP, and analysed using thematic analysis. Demographic, mood and PD related information was also collected to characterise the sample.

Results: Six major themes relating to help-seeking were identified in the sample: 1) causes of mood problems, 2) the meaning of depression and anxiety, 3) the source of help, 4) attitudes about treatment, 5) coping strategies, and 6) relationship with the clinician. Thematic differences between help seekers and non help seekers were identified.

Conclusion: Specific attitudes, knowledge and preferences to mood problems and treatment thereof were identified in this sample. Understanding how these factors facilitate or hinder help-seeking will allow us to develop interventions to encourage help-seeking behaviour and ultimately improve mood problems in these patients.

Disclosure: This research is supported by an East Kent Hospitals University NHS Foundation Trust R&D grant scheme.

P3235

Look, don't look, look close: video-oculographic abnormalities in functional movement disorders

M. Slovak[1], T. Serranova[1], T. Sieger[2], C. Bonnet[3], O. Ulmanova[1], J. Hanuska[1], E. Ruzicka[1]
[1]Charles University, First Faculty of Medicine and General University Hospital, Department of Neurology, Prague, Czech Republic, [2]Czech Technical University, Faculty of Electrical Engineering, Department of Cybernetics, Prague, Czech Republic, [3]Pierre and Marie Curie University, Paris, France

Background and aims: Convergence spasm (transient ocular convergence, miosis and accommodation associated with disconjugate gaze) was reported as a common eye movement (EM) abnormality in patients with functional (psychogenic) movement disorders (FMD). Our aim was to verify the incidence of convergence spasm and to further analyze EM abnormalities in FMD using videooculography (VOG). Additionally, we hypothesized that the antisaccade task may reveal a specific deficit in motor response inhibition in FMD.

Method: 8 female patients with FMD and 9 matched controls underwent VOG with tasks for prosaccades (rapid reflexive EM to the target point), antisaccades (rapid volitional EM to the opposite site from the target point) and vergence (alternation of convergence and divergence tracking proximal and distal target point). Latencies and mean saccade velocities were analyzed in prosaccades and vergence. In antisaccades, error rate (percentage of errors from total number of antisaccades) was evaluated.

Results: Only 1 out of 8 patients presented a convergence spasm during the EM examination. However, in comparison with controls, FMD patients showed prolonged latencies in both convergence and divergence ($P<0.05$), but no alterations in velocities in the vergence task, and higher error rate (44% vs 27%, $P<0.001$) in antisaccades. No differences in prosaccades were found.

Conclusion: Despite a low incidence of an overt convergence spasm, VOG revealed subclinical abnormalities in vergence EM along with normal reflexive EM in FMD. Consistently with current hypothesis of attention deficit and response inhibition disorders in FMD, we found an increased error rate in antisaccades in FMD.

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P3236

Psychiatric burden in patients with initial stage Parkinson's disease and early mild cognitive impairment

I. Stanković[1], A. Tomic[1], M. Ječmenica Lukić[1], N.D. Kresojevic[1], V. Marković[1], G. Mandic Stojmenovic[2], T. Stojkovic[2], N. Dragasevic[1], I. Petrović[1], M. Svetel[1], E. Stefanova[2], V. Kostic[1]

[1]Clinic of Neurology, Neurodegenerative diseases, Belgrade, Serbia, [2]Neurology Clinic, Clinical Centre of Serbia, Centre for memory disorders, Belgrade, Serbia

Background and aims: Psychiatric manifestations and mild cognitive impairment (MCI) became increasingly recognized in the early stage of Parkinson's disease (PD). We report a baseline cross-sectional assessment of psychiatric symptoms derived from a prospective cohort study of yearly followed-up PD patients recruited in the initial stage of PD (Hoehn and Yahr stage 1; HY1).

Methods: Non-demented PD outpatients in the HY1 stage (n=117) and sex and age-matched healthy controls (HC) (n=109) underwent detailed clinical, psychiatric and neuropsychological testing. Psychiatric evaluation consisted of depression, anxiety, apathy, perceptive problems and sleep and wakefulness assessments. MCI was diagnosed according to the level 2 of the Movement Disorders Society Task Force criteria.

Results: Initial-stage PD patients were more frequently depressed ($p<0.01$), anxious ($p<0.01$) and apathetic ($p<0.01$), with more cognitive ($p<0.01$) and sleep problems ($p=0.003$) compared to HC. Higher caregiver burden was associated with symptoms of depression ($p<0.01$), anxiety ($p<0.01$), apathy ($p<0.01$), sleep problems ($p<0.01$) and agitation ($p=0.039$). Criteria for MCI associated with PD (PD-MCI) were fulfilled in 24% of PD patients at the -1.5 SD, in contrast to 7% of MCI in HC group. PD-MCI patients at early disease endorsed depression ($p=0.014$) and anxiety ($p=0.022$) more frequently compared to PD-nonMCI patients. Sleep problems, including vivid dreams ($p=0.019$) and frequent waking ($p=0.036$), were more prevalent in MCI-PD group ($p=0.018$) compared to PD-nonMCI patients.

Conclusion: The major psychiatric burden in initial-stage PD-MCI patients are depression and sleep distrubances.

Disclosure: This study was supported by a grant from the Ministry of Education and Science, Republic of Serbia (projects No#175090).

P3237

Acetyl-dl-leucine for treatment of Niemann-Pick type C: a case series

T. Bremova[1], V. Malinova[2], Y. Amraoui[3], E. Mengel[4], J. Reinke[4], M. Kolnikova[5], M. Strupp[1]

[1]University Munich, Department of Neurology, Munich, Germany, [2]First Faculty of Medicine, Charles University, General University Hospital Prague, Department of Pediatrics and Adolescence Medicine, Prague, Czech Republic, [3]Center for Paediatric and Adolescent Medicine, University Medical Center of the Johannes Gutenberg University Mainz, [4]Department of Lysosomal Storage Disorder, Mainz, Germany, 44 Department of Lysosomal Storage Disorder, Center for Paediatric and Adolescent Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany, [5]5 Department of Child Neurology, Comenius University Children's Hospital, Bratislava, Bratislava, Slovakia

Background and aims: Niemann-Pick type C disease (NP-C) is a rare lysosomal storage disorder characterized by a combination of systemic, neurological and psychiatrical symptoms. The most prominent neurological sign is cerebellar ataxia. The current disease-specific therapy approved for NP-C miglustat slows the progression of the disease, however, additional symptomatic therapies are needed to improve the function and quality of life of NP-C patients. Acetyl-DL-leucine (AL), an amino acid, ameliorates cerebellar symptoms in patients with cerebellar ataxia. We evaluated the AL efficacy in NP-C patients.

Methods: 12 NP-C patients were treated with AL 3g/day for 1 and 5g/day for 3 weeks. The Scale for the Assessment and Rating of Ataxia (SARA), Spinocerebellar Ataxia Functional Index (SCAFI), modified Disability Rating Scale (mDRS), EuroQol 5Q-5D-5L and Visual Analog Scale (VAS) were administrated. Measurements took place at baseline, after 1 month of therapy, and after 1 month of wash-out.

Results: SARA significantly changed from baseline of 10.8 (8 to 24.6) to 7.0 (5.6 to 19.6) (median (IQR)) under medication and 10.5 (7.1 to 23.9) after wash-out ($p=0.000412$; post hoc $p=0.003$ between baseline and on medication, on medication and wash-out $p=0.005$). SCAFI subscore 9-Hole-Peg-Test (9HPT) for dominant hand, mDRS and VAS significantly improved under medication. No side effects in 11 patients, but intermittent vertigo in 1 patient were reported.

Conclusion: The treatment with AL significantly improved ataxic symptoms in NP-C patients without persistent side effects showing a good risk-benefit profile.

Disclosure: This study was supported by the BMBF to the IFB (grant code 01 EO 0901).

P3238

Dopa-responsive dystonia in the Serbian population: clinical and genetical characteristics

M. Svetel[1], A. Tomic[1], V. Dobricic[2], I. Novakovic[2], N. Dragasevic Miskovic[1], I. Petrović[1], V. Kostic[1]
[1]Institute of Neurology, Faculty of Medicine, University of Belgrade, Movement Disorders Department, Belgrade, Serbia, [2]Institute of Neurology, Faculty of Medicine, University of Belgrade, Laboratory for Molecular Genetic Diagnostic of Neurological Diseases, Belgrade, Serbia

Background and aims: Dopa-responsive dystonia (DRD) is inborn neuromethabolic disorders which could be inherited as an autosomal-dominant (AD) disease with heterozygous mutations in GPT-cyclohydrolase 1 gene (GCH1-DYT5a) and autosomal-recessive (AR) one with homozygous or compound heterozygous mutations in genes for thyrosin-hydrolase (TH) (DYT5b) or sepiapterin-reductase (SPR). AD form is characterized by reduced penetrance and excellent and permanent response to levodopa, while AR form is more severe, with developmental delay and cognitive impairment. The objecitve was to assess genetic and clinical characteristics of GCH1 mutations carriers in patients with dystonia-plus syndrome in Serbia.

Methods: The study comprised 66 patients with dystonia-plus syndrome and 60 healthy controls matched by age and gender. Genetical analysis was performed by direct sequencing of coding exones of GCH1 gene, and MLPA analysis for detection of large duplications/deletions.

Results: We found 5 point mutations (c.209delA, c.470T>C, c.541+1G>C, c.550C>T, c.608G>A) and one deletion of whole exon 2 in GCH1 gene in 10 carriers. The most frequent mutation (c.470T>C) was demonstrated in a family with 5 affected members, all with spastic paraparesis as initial presentation and excellent levodopa responsiveness. Phenotype spectrum was wide in our group of patients, from lower extremities dystonia to hemiparkinsonim, dystonia-parkinsonism complex and spastic paraparesis. All patients were on continuous levodopa treatment.

Conclusion: Our results showed GCH1 mutations in 15% of patients with dystonia-plus syndrome. It is important to stress phenotypic heterogeneity of the disease with wide spectrum of clinical expressions in forms of dystonia, parkinsonism and spastic paraparesis.

Disclosure: Nothing to disclose

P3239

Abstract cancelled

P3240

Botulinum toxin treatment of freezing of gait in Parkinson's disease patients as reflected in functional magnetic resonance imaging of leg movement

M. Vaštík[1], P. Hok[1], P. Hlustik[2], P. Otruba[3], Z. Tüdös[4], P. Kanovsky[5]
[1] Palacky University Medical School and University Hospital, Olomouc, Department of Neurology, Olomouc, Czech Republic, [2]Olomouc, Czech Republic, [3]University Hospital Olomouc, Neurology, Olomouc, Czech Republic, [4]Palacky University Medical School and University Hospital, Olomouc, Department of Radiology, Olomouc, Czech Republic, [5]University Hospital and Faculty of Medicine and Dentistry, Palacky University Olomouc, Neurology, Olomouc, Czech Republic

Background and aims: Freezing of gait (FOG) is a common disabling symptom in Parkinson's disease (PD). The mechanism of FOG in not clearly understood. We investigated the clinical effect and changes of the activity of the sensorimotor system using repeated functional MRI (fMRI) before and after application of botulinum toxin in Parkinson's disease patients with FOG.

Methods: We investigated 20 patients with PD, 10 with FOG and 10 without FOG. PD patients with FOG were treated with intramuscular application of botulinum toxin type A into the tensor fasciae latae muscle bilaterally. The clinical effect of treatment was assessed using FOG questionnaire, "Time up and go" test, UPDRS, Hoehn and Yahr staging, Clinical global impression scale. Activation of the sensorimotor system was studied using BOLD fMRI of the whole brain during repetitive abduction – adduction of each leg interleaved with rest. The clinical (in the FOG group) and imaging (in both groups) examination was repeated after a four-week interval.

Results: In the FOG group, the FOG questionnaire has shown a decline of scores after application of botulinum toxin that suggests possible effect of botulinum toxin on freezing of gait. In fMRI results, both groups manifested reduction of the sensorimotor network activated with leg movement, however, the FOG group also showed increased activation in cerebellar vermis and nuclei, in dorsal pons and in medulla after treatment.

Conclusion: Alleviation of the FOG in PD patients by botulinum toxin seems to be reflected in the functional participation of the cerebellum and its projections as seen by fMRI.

Disclosure: Supported by IGAMZ13575

P3241

Characterization of cognitive function and change of function in a population-based cohort to study non-motor-symptoms of Parkinson's disease

E.-J. Vollstedt[1], J. Graf[2], J. Hampf[2], S. Tunc[2], E. Warrlich[2], C. Bibergeil[2], C. Klein[2], M. Kasten[3]
[1]Institute of Neurogenetics, Lübeck, Germany, [2]University of Lübeck, Institute of Neurogenetics, Lübeck, Germany, [3]University of Lübeck, Clinic for Psychiatry and Psychotherapy, Lübeck, Germany

Background and aims: Cognitive function influences independency and is closely related to Parkinson's disease (PD). Various determinants have been indicated. We describe cognitive function and change in performance, comparing control groups and PD patients longitudinally.

Methods: After a population screening and baseline examination of 736 subjects including 119 PD patients, we re-examined 199 subjects, 61 PD patients and 41 subjects with mild Parkinsonian signs (MPS). Examination included the Montreal Cognitive Assessment (MoCA) with subscores for visuospatial, naming, recall, attention, language, abstraction, and orientation. Relative contribution of MoCA-subscores was defined as ratio subscore/summary score.

Results: At baseline, we analyzed determinants of MoCAscores in PD patients and subscore profiles across groups. We saw moderate correlation between MoCAscore and current age ($r=-0.279$, $p<0.001$), Hoehn&Yahr ($r=-0.274$, $p=0.005$), age at onset ($r=-0.251$, $p=0.009$), and disease duration ($r=-0.172$, $p=0.076$). Linear regression identified age at onset and disease duration as independent determinants ($R2=23.8\%$). Relative contribution of MoCA subscores differed between groups for naming (highest in PD), visuospatial (lowest in PD), recall (lowest in PD; $p<0.001$).
Longitudinally, change in MoCA summary scores differed between groups, with declining scores in PD and MPS (ANOVA $p=0.024$). Specifically, MoCAsubscores showed a decline in abstraction ($p=0.079$) and recall ($p=0.033$) for PD and MPS.

Conclusion: PD characteristics only partially explain MoCAscores. Despite its brevity the MoCA seems sensitive for differences between domains. Interestingly, even the MPS group had more cognitive decline than the control groups and showed similar development of subscores as the PD group.

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P3242

Levodopa response in paroxysmal exercise-induced dystonia without GLUT1 deficiency

B. Ziso, A. Larner
Walton Centre Neurology and Neurosurgery, Neurology, Liverpool, United Kingdom

Background and aims: To report a patient with paroxysmal exercise-induced dystonia complicated by severe intention upper limb and head tremor, and the tremor response to levodopa.

Methods: A prospective observational study, Cognitive Function Clinic.

Results: Episodes of painless flaccid limb weakness after exercise, accompanied with bending truncal movements and dystonic hand movements lasting for hours, began at age 18 months but became infrequent by age 30 years. From age 5 years, bilateral optic atrophy and pendular nystagmus developed, and as a teenager typical migraine with aura. In her mid-thirties she developed upper limb intention tremor and head tremor making it difficult to feed herself. Intellect was preserved (6CIT = 0/28).
Genetic testing showed no pathogenic sequence variant or copy number change in the SLC2A1 gene, hence there was no evidence for GLUT1 deficiency. Mitochondrial point mutations associated with MELAS, MERFF, NARP, and LHON (3243, 8344, 8993; 3460, 11778, 14484) were all negative, as was Friedreich's ataxia triplet expansion. Levodopa (300 mg/day) improved her limb tremor, such that she was able to feed herself.

Conclusion: Some cases of paroxysmal exercise-induced dystonia without GLUT1 deficiency may show a partial response to levodopa therapy.

Disclosure: Nothing to disclose

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P3243

Demography, clinical characteristics and socioeconomic status of the Portuguese patients with multiple sclerosis in 2014 – results of the national cross-sectional PORT-MS study

J. Tomás[1], J. Dias Ferreira[2], J. Sequeira[3], M. Grilo[4], R. Samoes[5], S. Varanda[6], J. Morgado[3], J. Guimaraes[4], C. Nunes[1], J.J.F.C.A. Cerqueira[6], J.M. Vale Santos[7], M.J. Sá[8], A.A.D.M. Silva[5], L.M.A.F.D. Sousa[1], R.M.G. Pedrosa[3], J. de Sa[2], P. Alegria[7]

[1]Centro Hospitalar Universitário de Coimbra, Neurology, Coimbra, Portugal, [2]Centro Hospitalar de Lisboa Norte – Hospital de Santa Maria, Neurology, Lisbon, Portugal, [3]Centro Hospitalar de Lisboa Central – Hospital de Santo António dos Capuchos, Neurology, Lisbon, Portugal, [4]Centro Hospitalar de São João, Neurology, Porto, Portugal, [5]Centro Hospitalar do Porto – Hospital de Santo António, Neurology, Porto, Portugal, [6]Hospital de Braga, Neurology, Braga, Portugal, [7]Hospital Beatriz Ângelo, Neurology , Loures, Portugal, [8]Centro Hospitalar de São João, Neurology , Porto, Portugal

Background and aims: In Portugal, there did not exist a multicentric study on the general characteristics (demography, disease milestones, disease modifying treatment (DMT), socioeconomic status) of multiple sclerosis (MS) patients.

Methods: Patients fulfilling McDonald 2010 criteria were sequentially recruited from May to November 2014 in 7 centers and data was systematically collected.

Results: 561 patients included: first symptoms occurred at 30.2±10.5 years old (Relapsing Remitting (RR) MS 29.2±10, Primary Progressive (PP) MS 39.4±11.7, p<0.001); diagnosis 3.2±5.3 years later (RRMS 3.0±5.1, PPMS 4.9±2.5, p=0.002); 9.4±7.2 years elapsed since diagnosis (similar RRMS and PPMS); current age 42.9±12.4 years-old (RRMS at diagnosis 42.0±12.1, PPMS 52.5±11.3, p<0.001); current EDSS 2.5 (RRMS 2.0, PPMS 6.0); females to males 2.5:1 (RRMS similar, PPMS 1.1:1, p<0.05); at diagnosis RRMS 90.6%, SPMS 0.9%, PPMS 8.6%; 9.5% of RRMS reached SP at inclusion (those older at diagnosis, in actuality, or with longer follow-up); proportion on DMT 90.4% of currently in RRMS; Economically active 61.5% of all, unemployment 13.5%; females pregnant after diagnosis 15%; positive family cases in 7.8%. Analysis by age at diagnosis: PPMS more frequent at older ages (p<0.001), also slight increase in females. Analysis by diagnosis at each of the last decades: stable proportions of gender and disease types.

See Table for additional data.

Result	Value	Additional data
Patients on DMT in May 2014	84,5%	90,4% of currently in RRMS; 70,8% of SPMS; 36,8% of PPMS; 48% of progressive forms together. Type of DMT: interferons 56,5%, Glatiramer Acetate 18,4%, Natalizumab 11,6%, Fingolimod 9,7%.
Economically active	61,5%	13,5% of active are unemployed. 74,1% of non-active population are retired due to disease.
Analysis by diagnosis at each of the last decades		Age at first symptoms and diagnosis slightly increased, time between them slightly decreased.

Table: additional data.

Conclusion: 10% of the national MS population was collected. Data generally consistent with international reports. Proportion under DMT relatively high in all disease types, but second line therapies underrepresented. Young patients with mild disease have an active economic life. Those not active are essentially retired due to disease.

Disclosure: This research had institucional support from Biogen Idec and the GEEM (Grupo de Estudos de Esclerose Múltipla, the Portuguese medical society for MS)

P3244

Cognition in neuromyelitis optica: a systematic review

F. Trew[1], K. Murray[2], S. Pal[2]
[1]University of Edinburgh, Edinburgh, United Kingdom, [2]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom

Background and aims: Neuromyelitis Optica (NMO) is an antibody-mediated central nervous system disorder characterised by optic neuritis and longitudinally extensive transverse myelitis. Whilst clinically similar to multiple sclerosis (MS), it has been widely assumed cognition is spared. However, recent case series have reported deficits in attention, information processing speed and memory. This systematic review and narrative analysis evaluates cognitive performance in NMO, and compares profiles with healthy controls and patients with MS.

Methods: A wide-ranging literature search was conducted using the Medical Subject Headings Neuromyelitis Optica, Cognition, Cognitive Disorders and Memory from 2004-2014.

Results: 6 studies fulfilled inclusion criteria, including 129 patients with NMO, 61 with MS, and 158 healthy controls. Neuropsychological tests used included the Brief Repeatable Battery of Neuropsychological Tests and the California Verbal Learning Test. Patients were matched for age, education, disease course and severity. All studies demonstrated significant cognitive impairment in patients with NMO compared to controls. Profiles of deficit varied, but memory impairment was uniformly identified. Impaired information processing speed and attention were present in most, and impaired executive function, learning and verbal fluency in individual studies. There was no significant difference between NMO and MS.

Conclusion: Patients with NMO demonstrate significant cognitive impairment similar in severity to MS. This is potentially functionally impairing, under-recognised, and incompletely evaluated suggesting that NMO patients should be counselled accordingly and symptoms screened for. Larger studies are warranted using more versatile cognitive tests and controlling for common confounders, to assess if clinical phenotype or MRI changes predict cognitive deficits.

Disclosure: Nothing to disclose

P3245

The MS@Work study – predictors of employment status and work absenteeism in relapsing-remitting Multiple Sclerosis

D. van Gorp[1], K. van der Hiele[2], M. Heerings[1], P. Jongen[3], I. van Lieshout[4], F. Vosman[5], M. Reneman[6], J. van der Klink[7], H. Middelkoop[2], L. Visser[8]
[1]National MS Foundation, Maassluis, The Netherlands, [2]Leiden University, Leiden, The Netherlands, [3]MS [4] Research Institute, Nijmegen, The Netherlands, [4]Van Lieshout Arbo Advies, Uden, The Netherlands, [5]University of Humanistic Studies, Utrecht, The Netherlands, [6]University Medical Center Groningen, Haren, The Netherlands, [7]Tilburg University, Tilburg, The Netherlands, [8]St. Elisabeth Hospital, Tilburg, The Netherlands

Background and aims: The majority of Multiple Sclerosis (MS) patients are unable to retain employment within 10 years from disease onset. Cross-sectional studies have identified factors associated with decreased employment status and work absenteeism in MS, including cognitive, physical and psychological problems, work factors and type of treatment. Prospective studies are rare, or take into account a limited number of factors. The main aim of this study is to examine predictors of (changes in) employment status and work absenteeism in relapsing-remitting MS (RRMS) patients over a period of three years. In a sub study 20 semi-structured interviews will be conducted to examine patient perspectives on what can be done to improve work participation.

Methods: The MS@Work study is an observational, prospective cohort study in 400 patients with RRMS recruited from 15 outpatient clinics in the Netherlands. We plan to include RRMS patients who are 18 years and older, and either currently employed or within three years since their last employment. At baseline and after 6 months, 1, 2 and 3 years, participants will be asked to complete occupational and psychological questionnaires, and undergo neurological and neuropsychological examinations.

Results: At abstract submission, 63 patients have been recruited. Baseline characteristics will be presented. Final data are expected in 2018.

Conclusion: The study will provide more insight in the predisposing factors resulting in decreased work participation in patients with MS. Possible factors, like (perceived) cognitive problems, fatigue, depression, coping style and physical disability are factors which could be addressed by healthcare professionals working in occupational health.

Disclosure: This research is financially supported by the National Multiple Sclerosis Foundation, the Netherlands, Teva Pharma BV and by a ZonMw TopZorg grant.

P3246

InMS: Chronic Insomnia Disorder in Multiple Sclerosis – a Portuguese multicentre study on prevalence, subtypes, associated factors and impact on quality of life

P. Viana[1], E. Rodrigues[2], C. Fernandes[3], A. Matas[4], R. Barreto[5], M. Mendonça[6], R. Peralta[7], R. Geraldes[8]
[1]Lisbon, Portugal, [2]Centro Hospitalar do Funchal, Neurology Department, Funchal, Portugal, [3]Hospital Garcia de Orta, Neurology Department, Almada, Portugal, [4]Centro Hospitalar Trás-os-Montes e Alto Douro, Neurology Department, Vila Real, Portugal, [5]Centro Hospitalar Entre-o-Douro e Vouga, Neurology Department, Santa Maria da Feira, Portugal, [6]Centro Hospitalar Lisboa Ocidental, Neurology Department, Lisbon, Portugal, [7]Hospital de Santa Maria, Neurology Department, Lisbon, Portugal, [8]Oxford University Hospital, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom

Background: Patients with Multiple Sclerosis (MS) have under-recognized sleep disorders and frequent sleep complaints. Few studies have addressed insomnia using standard diagnostic criteria in MS patients.

Objectives: To determine the prevalence of chronic insomnia disorder (CID) in a population of MS patients, the frequency of CID subtypes, identify associated factors and assess impact on quality of life (QoL).

Methods: Hospital-based, multicentre, cross-sectional study of an MS population, in order to assess CID, as defined by the 3rd Edition of the International Classification of Sleep Disorders, using an adapted version of the Brief Insomnia Questionnaire. This instrument was also used to classify CID subtypes. A comprehensive questionnaire was used to evaluate demographic, MS-related features as well as other possible contributors to CID. Fatigue was evaluated by the Fatigue Severity Scale. QoL was assessed by the EQ-5D scale.

Results: Of 206 patients, 39.3% complained of frequent insomnia symptoms, while 22.3% fulfilled criteria for CID. Initial insomnia was found in 11.7%, maintenance insomnia in 11.2% and terminal insomnia in 10.2% of patients. CID was significantly more common in female patients, those with nocturnal symptoms and other medical comorbidities, and correlated with higher levels of anxiety, depression and fatigue. Multivariate analysis identified female sex, medical comorbidities, anxiety and fatigue as independent factors for CID. CID patients had a significantly lower self-reported QoL.

Conclusion: CID is prevalent in MS patients and highly associated with potentially treatable psychiatric and medical comorbidities. It is also associated with fatigue and has a negative impact on QoL.

Disclosure: Nothing to disclose

P3247

Investigating the spectrum of cognitive impairment in multiple sclerosis using touchscreen cognitive testing

N. Vithanage[1], K. Murray[2], S. Colville[2], D. Lyle[2], D. Cranley[2], F. Cormack[3], J. Barnett[3], S. Pal[2]
[1]University of Edinburgh, Edinburgh, United Kingdom, [2]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom, [3]Cambridge Cognition, Cambridge, United Kingdom

Background and aims: Multiple sclerosis (MS) is a CNS demyelinating syndrome characterised by physically disabling symptoms. Cognitive impairment, which potentially impact on quality of life, is generally under-recognised and incompletely evaluated but has been reported in up to 70% of patients when specifically assessed.

The aims were to investigate the spectrum of cognitive impairment, and potential confounding factors for deficits, in patients with MS reviewed in an outpatient clinic using validated Cantab neuropsychological tests administered by touchscreen.

Methods: 105 consecutive patients presenting to a specialist MS clinic were assessed. Working Memory (WM), Executive Functioning (EF), Processing Speed (EF), Attention (AT) and Episodic Memory (EM) were evaluated using the Cantab mobile test. Performance was adjusted for age, sex and educational level based on a large normative database. Disease duration, type of MS, severity of disease, sedating medications, and severity of depression were correlated with the presence and severity of cognitive deficits.

Results: The most frequent cognitive domain affected was EF (in 25%), followed by WM (23%), PS (17%), EM (18%) and AT (6%). Single domain cognitive impairment was identified in 24% of patients and multi-domain deficits in 26%. Disease severity was associated with impaired WM, EF, PS and AT. Severity of depression correlated with diminished EF, WM and PS.

Conclusion: Results from this study confirm cognitive impairment is common in MS patients. Furthermore, impairment occurs across a range of domains, and correlates with disease duration although is independent of factors such as age and type of MS. Routine testing is recommended as part of holistic patient assessment.

Disclosure: Nothing to disclose

P3248

Cerebrospinal fluid free light chains are elevated in clinically isolated syndrome and multiple sclerosis and correlate with lesion load and cortical thinning

M. Voortman, T. Stojakovic, M. Jehna, H. Scharnagl, S. Ropele, T. Seifert-Held, J.J. Archelos-Garcia, S. Fuchs, C. Enzinger, F. Fazekas, M. Khalil
Medical University of Graz, Graz, Austria

Background and aims: It has been shown that cerebrospinal fluid (CSF) immunoglobulin free light chains (FLC) are increased in multiple sclerosis (MS). However, only scarce information exists regarding their relation to MRI metrics, in particular measures of brain changes in regions with direct contact to CSF.

We thus aimed to compare FLC kappa (KFLC) and FLC lambda (LFLC) levels in CSF and serum between MS patients and controls, and to investigate their relation to MRI based measures of cortical thinning and periventricular lesion load.

Methods: FLC in CSF and serum were measured by nephelometry in 61 patients (clinically isolated syndrome (CIS) n=48, relapsing-remitting MS n=13) and 60 non-inflammatory neurologic controls. We then calculated CSF/serum FLC quotients and determined FLC indices by correcting for the albumin quotient. CIS/MS patients underwent MRI at 3T to determine the extent of cortical thinning (FreeSurfer software) and periventricular lesion load.

Results: In MS we found increased CSF KFLC and LFLC levels, quotient and indices compared to controls ($p<0.001$). CSF LFLC correlated with the percentage of periventricular lesion load ($r=-0.356$, $p=0.005$) and the CSF KFLC index correlated with mean cortical thickness ($r=0.274$, $p=0.036$). No correlation emerged between CSF FLC and physical disability.

Conclusion: Our study demonstrates increased intrathecal synthesis of KFLC and LFLC in MS emphasizing an altered B-cell response. The correlation of FLC with MRI based measures of cortical and periventricular tissue damage suggests an etiologic association. Further studies with longitudinal clinical and MRI data are necessary to confirm our findings.

Disclosure: Nothing to disclose

P3249

Economic costs of an MS relapse (PEARL Study)

S. Vormfelde[1], T. Ziemssen[2]
[1]Novartis Pharma GmbH, TA Neuroscience, Nuremberg, Germany, [2]Carl Gustav Carus University Hospital, Center for Clinical Neurosciences, Dresden, Germany

Background and aims: There is an ongoing discussion, whether medical, patient and healthcare cost caused by relapses warrant early escalation of pharmacotherapy. Here we focus on healthcare cost.

Methods: The PEARL study (ProspEctive phArmacoeconomic cohoRt evaLuation) is a 24-month, German non-interventional study in 1705 patients with relapsing remitting multiple sclerosis (RRMS). Patients were treated office-based, 1214 with beta-interferons, 491 with glatiramer acetate. To describe the costs of a relapse, we compare patients with a relapse in the first study year (ACTIVE group) to those without (INACTIVE group).

Results: In the first study year, 411 patients relapsed at least once (ACTIVE group, "A"); 1294 patients did not relapse (INACTIVE group, "I"). Mean MS-duration was 5.1 and 5.2 years in ACTIVE and INACTIVE patients, respectively. The mean annual relapse rates over the two year period were A=1.4 and I=0.1 relapses/year. Employment declined only in the ACTIVE group during the two year period (A:58%→53%, I:61%→61%). Also more ACTIVE patients were permanently part-time employed (A: 7%→5%, I:6%→2%), with lower fractions of full employment at study end (A:50%→35%, I:53%→56%). Only ACTIVE patients continuously felt their work productivity suppressed by MS (A:2.2→2.3, I:2.1→1.7, 0-10 rating scale). More ACTIVE patients took sick leaves at baseline as well as at the end of the study (A: 33%→18%, I: 18%→8%, [of patients/quarter]), were hospitalized (A:7.1%→3.3%, I:4.0%→1.2%, [of patients/quarter]) or stayed in rehabilitation (A:2.7%→1.4%, I:1.8%→1.0%, [of patients/year]).

Conclusion: MS patients are less productive in the year following a relapse.

Disclosure: The PEARL study was supported by Novartis Pharma GmbH, Nuremberg, Germany; Stefan Vormfelde ist employee of Novartis; Tjalf Ziemssen has served on scientific advisory boards, and has received scientific grants and speaker honoraria from Bayer, Biogen Idec, Genzyme, TEVA, Merck Serono, and Novartis.

P3250

Disability, health status and estimation of treatment effectiveness with versus without an MS relapse (PEARL Study)

S. Vormfelde[1], T. Ziemssen[2]

[1]Novartis Pharma GmbH, TA Neuroscience, Nuremberg, Germany, [2]Carl Gustav Carus University Hospital, Center for Clinical Neurosciences, Dresden, Germany

Background and aims: There is an ongoing discussion, whether medical, patient and healthcare costs caused by relapses warrant early escalation of pharmacotherapy. Here we focus on the medical perspective.

Methods: The PEARL study (ProspEctive phArmacoeconomic cohoRt evaLuation) is a 24-month, German non-interventional study in 1705 patients with relapsing remitting multiple sclerosis (RRMS). Patients were treated office-based, 1214 with beta-interferons, 491 with glatiramer acetate. To describe the costs of a relapse, we compare patients with a relapse in the first study year (ACTIVE group) to those without (INACTIVE group).

Results: In the first study year, 411 patients relapsed at least once (ACTIVE group, "A"); 1294 patients did not relapse (INACTIVE group, "I"). Mean MS-duration was 5.1 and 5.2 years in ACTIVE and INACTIVE patients, respectively. The mean annual relapse rate was 1.4 and 0.1 relapses/year over the two year period, respectively.

Disability, measured by the Expanded Disability Status Scale (EDSS), was worse in ACTIVE patients at baseline and deteriorated further during the 24 months (A:2.5→3.0, I:2.2→2.4).

Health worsening peaked in ACTIVE patients in the first study year and then remained elevated (CGI improvement scale, fraction who reportedly worsened minimally, much or very much compared to the previous year at baseline/peak/24 months: A:23%/32%/16%, I:6%/8%/10%).

ACTIVE patients switched drug more often (A:30%, I:12%). Physicians and patients deemed treatment similarly effective; except those INACTIVE patients, who later discontinued treatment, more often thatn their physicians deemed treatment insufficient (30% vs 19%).

Conclusion: Patients remain worsened after a relapse. Intensifying therapy may reduce such worsening.

Disclosure: The PEARL study was supported by Novartis Pharma GmbH, Nuremberg, Germany; Stefan Vormfelde ist employee of Novartis; Tjalf Ziemssen has served on scientific advisory boards, and has received scientific grants and speaker honoraria from Bayer, Biogen Idec, Genzyme, TEVA, Merck Serono, and Novartis.

P3251

The Patient's subjective consequences of an MS relapse (PEARL Study)

S. Vormfelde[1], T. Ziemssen[2]

[1]Novartis Pharma GmbH, TA Neuroscience, Nuremberg, Germany, [2]Carl Gustav Carus University Hospital, Center for Clinical Neurosciences, Dresden, Germany

Background and aims: There is an ongoing discussion, whether medical, patient and healthcare costs caused by relapses warrant early escalation of pharmacotherapy. Here we focus on the patient perspective.

Methods: The PEARL study (ProspEctive phArmacoeconomic cohoRt evaLuation) is a 24-month, German non-interventional study in 1705 patients with relapsing remitting multiple sclerosis (RRMS). Patients were treated office-based, 1214 with beta-interferons, 491 with glatiramer acetate. To describe the costs of a relapse, we compare patients with a relapse in the first study year (ACTIVE group) to those without (INACTIVE group).

Results: In the first study year, 411 patients relapsed at least once (ACTIVE group, "A"); 1294 patients did not relapse (INACTIVE group, "I"). Mean MS-duration was 5.1 and 5.2 years in ACTIVE and INACTIVE patients, respectively. The mean annual relapse rate was 1.4 and 0.1 relapses/year over the two year period, respectively. Over the 24-month study period, treatment satisfaction declined only in ACTIVE patients (A:54%→36%, I:52%→55%). Subjective health state as measured by the EQ-5D scale deteriorated only in ACTIVE patients (A:69.9→68.0, I:72.0→73.2). ACTIVE patients were worse off after 24 months in all five EQ-5D dimensions. E.g. 55% ACTIVE and 41% INACTIVE patients had pain or discomfort after 24 months (baseline 52%/49%). MS-specific subjective quality of life impairment was greater and declined less in ACTIVE patients (A:8.7→7.8, I:8.3→6.8). MS-specific subjective activity impairment was greater and worsened more in ACTIVE patients (A:4.7→5.0, I:4.0→4.1).

Conclusion: Activity and QoL worsen with a relapse. Escalating therapy may prevent such worsening.

Disclosure: The PEARL study was supported by Novartis Pharma GmbH, Nuremberg, Germany; Stefan Vormfelde ist employee of Novartis; Tjalf Ziemssen has served on scientific advisory boards, and has received scientific grants and speaker honoraria from Bayer, Biogen Idec, Genzyme, TEVA, Merck Serono, and Novartis.

Muscle and neuromuscular junction disease 2

P3252

Reduced activation of frontal and midline brain structures: new insight in the brain of myotonic dystrophy type 1 (DM1)

S. Baldanzi[1], C. Simoncini[2], G. Ricci[3], L. Volpi[2], P. Cecchi[4], S. Fabbri[4], G. Migaleddu[4], M. Cosottini[5], R. Lorio[6], F. Bevilacqua[6], A. Petrucci[7], C. Angelini[8], G. Siciliano[1]
[1]Pisa, Italy, [2]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [3]University of Pisa, Pisa, Italy, Department of Clinical and Experimental Medicine, Neurological Clinic, , Pisa, Italy, [4]Pisa Hospital, Neuroradiology Unit, Pisa, Italy, [5]Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy, Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy, Pisa, Italy, [6]IRCCS San Camillo, Neurology Unit, Lido Venice, Italy, [7]San Camillo Forlanini Hospital, Neurology Unit, Rome, Italy, [8]San Camillo Forlanini Hospital, Neurology Unit, Lido Venice, Italy

Background and aims: DM1 is a genetic multisystemic disorder due to polynucleotide expansions, characterized by functional/morphological brain abnormalities to different extents beyond muscular involvement.

Methods: 46 patients with established clinical-genetic diagnosis were enrolled in the frame of a larger study and underwent complete neurological assessment including psychological and neuropsychological evaluation, with the administration of quality of life interview to both, patient and main caregiver; 27 patients underwent brainMRI with 3T-scanner and a subgroup of 19 patients underwent functional MRI investigation during a validated self-awareness task based on self or semantic word attribution.

Results: Neurological examination showed mild to severe muscle involvement (MIRS mean2.98±0.92). Frontal and visuo-spatial abilities were reduced respectively in 61% and 66% of our patients; patients' behavior was characterized by anxiety, depression, apathy and by variable sets of pathological personality traits; illness-unawareness, assessed by the comparison between patient's and main caregiver's reports on quality of life, was found in 52.1% and was smoothly correlated with executive impairment ($p=0.075$). Parietal lobe white matter changes correlated with reduced spatial memory performances (Fisher-Exact-Test $p<0.05$). fMRI analysis revealed frontal and midline brain regions hypoactivation in patients with reduced illness-unawareness (Z-threshold>5.3,cluster p threshold <0.001).

Conclusion: In our study DM1 brain changes were both structural and functional, with functional impairment characterized by typical cognitive-behavioural disorders, with heterogeneous associations with clinical features. The association between illness-unawareness and specific brain regions hypoactivation may be a persistent deficit in subjects with DM1, thus representing a distinctive feature of this complex disease.

Disclosure: AFM (Association Francaise contre les Myopathies) research grant in 2012

P3253

DNAJB6 myopathy in a Saudi family with cytoplasmic and nuclear inclusions

S. Alfawaz[1], H. AlHindi[2], D. Monies[3], H. Murad[4], S. Bohlega[4]

[1]KFSH & RC, Neurosciences, Riyadh, Saudi Arabia, [2]KFSH & RC, Pathology & Laboratory Medicine, Riyadh, Saudi Arabia, [3]KFSH & RC, Genetics, Riyadh, Saudi Arabia, [4]Riyadh, Saudi Arabia

Background and aims: Limb Girdle Muscular Dystrophy (LGMD) is a clinically and genetically heterogeneous group of disorders. Recently a mutation in the DNAJB6 gene has been described in patient with LGMD1D. This is a rare disorder only recently described.

Objective: To describe the clinical feature, pathological finding and genetic results of a native Saudi family with LGMD1D.

Methods: Sixty-six (66) Saudi Arabian families with LGMD were recruited and the causative underlying genes were studied utilizing a genome wide linkage, homozygosity mapping, and whole exome sequencing.

Results: A Bedouin (nomads) native Saudi family: the father and one of his sons were affected. Progressive proximal weakness was noted at the age of 25 and at 17 in the son. The weakness led to being wheel-chaired at age of 40 with dysphagia and dysphonia requiring permanent tracheostomy in the father. The creatinine kinase levels were 2 to 3 times normal. Muscle biopsy showed marked variation in myofiber size with scattered angular atrophic fiber, nicotic fibers and myophagocytocis, and red-rimmed vacuoles depicting a sarcoplasmic bodies on trichrome-stained section. Heterozygous mutation in the exome 5 of DNAJB6, c. C287T predicting P96L were found in all affected.

Conclusion: DNABJ6 myopathy or LGMD1D is rarely identified in a large cohort from Arabic descent. The phenotype and the mutation described are different than those seen in other ethnic groups and our findings will expand the phenotype and genotype of this disorder.

Disclosure: Nothing to disclose

P3254

Mutations causing limb-girdle muscular dystrophy in the Polish population

J.P. Fichna[1], A. Macias[2], M. Szymczyk[2], A. Kaminska[2], C. Zekanowski[1]

[1]Mossakowski Medical Research Centre, Department of Neurodegenerative Disorders, Warsaw, Poland, [2]Medical University of Warsaw, Department of Neurology, Warsaw, Poland

Background and aims: Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of genetically determined disorders, characterized by primary or predominantly proximal distribution of muscle weakness. Individual LGMD subtypes are classified on the basis of genetics and so far 25 different loci associated with the disease have been identified. However, a large overlap of phenotypic manifestations resulting from different gene mutations poses a challenge for determination of the exact type of the muscular disease.

Methods: To accelerate molecular diagnosis and to widen spectrum of analysed genes we determined sequence of the exome, using Whole Exome Sequencing method.

Results: So far we have analysed genomic DNA samples from 21 LGMD patients, and in 15 cases (71%) we found mutations in the genes already associated with the disease. Homozygous or compound heterozygous mutations were detected in the following genes: CAPN3 (33% of all LGMD cases), DYSF (19%), FKRP (9.5%), ANO5 (9.5%), and PLEC1 (4%). 2 patients had more than one known gene affected. In total we have found 19 variants (both novel and already described) in LGMD associated genes with CAPN3 c.550delA being the most common (2 homozygotes and 4 heterozygotes). Apart from causative mutations also additional variants in genes related to muscle diseases were found: SGCA, TTN, DES, COL6A2, COL6A3, LDB3/ZASP, RYR1, LMNA, LARGE, NEB, FLNC. Those mutations could be modifiers of the clinical phenotype.

Conclusion: Genetic etiology of patients without mutations in already known LGMD genes is being further investigated.

Disclosure: The research was supported by the KNOW-MMRC project (JPF).

P3255

Long-term prognostic factors in ocular myasthenia gravis (OMG)

M. Mazzoli[1], A. Ariatti[1], M. Tondelli[2], F. Benuzzi[3], F. Valzania[1], P. Nichelli[3], G. Galassi[1]

[1]University of Modena, Biomedical,metabolic,neural sciences, Modena, Italy, [2]Universityof Modena, Biomedical, metabolic,neural sciences, Modena, Italy, [3]University of Modena, Biomedical, metabolic,neural sciences, Modena, Italy

Background and aims: Clinical expressions of Myasthenia Gravis (MG) ranges from limited ocular involvement to respiratory failure. Purpose of our study was to identify prognostic factors in our prospective cohort of 200 patients affected by ocular MG (OMG) evaluated during a follow-up period of 15 years.

Methods: Myastenia Gravis Foundation of America classification was used to grade disease severity every 6 months. Prognostic factors were gender, age at onset, electrophysiological results, presence of antibodies against acetylcholine receptors (AChR-Abs), treatment, thymic abnormalities. As outcome measures, we considered variations in ocular (O-QMG) or total (T-QMG) subscores, progression to generalizatio, changes in mental (MCS), physical (PCS) scores of SF-36.

Results: 115 cases were males, 85 females. Median age was 65 y. Patients with onset before 50 were considered early onset, the remaining 162 patients (81.0%) had late onset. Electrophysiological tests were positive in 66%.Anti-AChR-Abs were found in 39%. 11 patients had thymoma, 10 underwent thymectomy, 11% had hyperplastic thymus. 83% of patients received treatment. Generalization occurred within median time of 34 months in 20% of cases.

Conclusion: Among ocular scores, ptosis significantly worsened (p=0.004). No statistically significant changes were observed in MCS and PCS (p=0.71 0.42 respectively). Survival analyses showed that factors influencing generalization were age of onset and treatment (longer stability in younger treated patients, p=0.01).Patients with anti-AChR-Abs above mean value of 29.5 pmol/ml had high risk of generalization (p=0.001)confirmed on multivariate analysis (HR 3.67, 95%CI 1.35-9.9).Patients aged more than 50 had higher risk of worsening (HR 3.00, 95% CI 1.2-7.1) than younger subjects.

Disclosure: Nothing to disclose

P3256

LMNA-related congenital muscular dystrophy whole-body MRI fingerprint: description and comparison with SEPN1-related myopathy

D. Gómez Andrés[1], K. Hankiewicz[2], A. Felter[3], B. Doré[3], I. Dabaj[2], B. Estournet[2], P. Richard[4], R.Y. Carlier[3], S. Quijano-Roy[2]

[1]Hospital Universitario La Paz, Pediatric Neurology, Madrid, Spain, [2]Hôpital Raymond Poincaré, Centre de Référence Maladies Neuromusculaires GNMH. Service de Pédiatrie, Garches, France, [3]Hôpital Raymond Poincaré, Service de Radiologie, Garches, France, [4]GH Pitié-Salpêtrière, Inserm, UMRS_974, 4) U.F. Cardiogénétique et Myogénétique, Service de Biochimie Métabolique, Paris, France

Background and aims: Congenital muscular dystrophies (CMD) are genetically heterogeneous disorders. Molecular diagnosis is important for genetic counselling and clinical care but it may be difficult to establish due to overlapping clinical and histological features. Whole-body MRI (WBMRI) could be a complementary test to orientate diagnosis. We aim to define the fingerprint of muscle affection in LMNA-related CMD (L-CMD) and to compare it with the pattern described in SEPN1-related myopathy (SEPN-RM).

Methods: Signal abnormality and atrophy in 109 muscles using T1 weighthed WBMRI technique were scored by semiquantitative scales in 8 L-CMD patients. Heatmaps were used to represent the muscle involvement. Comparison with the pattern shown by 9 SEPN1-RM patients was made using conventional and regularized random forests.

Results: LMNA patients showed predominant signal abnormalities in the erector spinae, serratus anterior, subscapularis, gluteii medius and minimum, vastii, adductor magnus and longus, semimembranosus, medial gastrocnemius and soleus muscles.

In addition, atrophy was observed in the glutei medius and minimum muscles as well as the scapular girdle and tensor fascia latae. Head muscles, flexor digitorum longus, and tibialis posterior muscles tended to be spared. Psoas, sternocleidomastoid, gracilis and sartorius muscles were often preserved from infiltration although sometimes atrophied.

Random forest revealed that atrophy and infiltration of gluteus minimum, atrophy of sternocleidomastoid and particularly, atrophy of semimembranosus were the most relevant muscles to distinguish between L-CMD and SEPN1-RM.

Conclusion: WBMRI shows a selective pattern in children with L-CMD. Artificial intelligence techniques identified a reduced number of muscles of interest in the differential diagnosis between this entity and SEPN1-RM.

Disclosure: This work was financially supported by the Assistance Publique des Hôpitaux de Paris (APHP), Institute Nationale de la Santé (INSERM), Université de Versailles Saint Quentin-en-Yvelines (UVSQ) and Ministerio de Sanidad (España).

P3257

Single referral center study in Serbia: a case series of 41 patients with congenital myasthenic syndromes

A. Kosac[1], V. Milic Rasic[2], J. Mladenovic[1], S. Todorovic[3], G. Vlahovic[4], V. Rakocevic Stojanovic[5], D. Savic Pavicevic[6], H. Lochmuller[7]

[1]Clinic for neurology and psychiatry for children and youth, Belgrade, Serbia, [2]Clinic for neurology and psychiatry for children and youth, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [3]Clinic for neurology and psychiatry for children and youth, Belgrade, Serbia, [4]Mother and Child Health Care Institute, Belgrade, Serbia, Department of Neurology, Belgrade, Serbia, [5]Clinic of neurology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [6]Faculty of Biology, University of Belgrade, Belgrade, Serbia, [7]Institute of Genetic Medicine, Newcastle University, Newcastle, United Kingdom

Background and aims: Congenital myasthenic syndromes (CMS) are rare, heterogeneous group of disorders which are caused by inborn defect of the structure/ function of the neuromuscular junction. The aim of this study was to present both clinical and genetic characteristics of the series of patients with CMS.

Methods: A retrospective study based on the patient's medical records examined and treated in the clinic under suspicion of CMS in the period between 2000 and 2014. Diagnosis of CMS was established after carrying out necessary clinical and electrophysiological examinations. All patients were analyzed at the genetic level. The descriptive statistical model was applied.

Results: 41 patients (21 male and 20 female), from 28 families, were diagnosed with CMS. Diagnosis of CMS was defined at the genetic level in 32 (78%), out of which 31 with postsynaptic CMS, 1 with synaptic CMS and no patients with presynaptic CMS. Positive neostigmine test was observed in 38 out of 40 patients. Repetitive nerve stimulation test was positive in 18 out of 29 tested patients. Among patients with postsynaptic CMS, 26 were diagnosed with CHRNE (1267delG), 3 with RAPSN and 2 patients with CHRNB1. All patients with 1267delG mutation were gypsies, and had ptosis, ophthalmoparesis and pathological fatigability; delayed psychomotor development had 42%; non/ slowly progressive course of the disease 92% and 77% of patients showed good clinical response to pyridostigmine.

Conclusion: Results suggest possible algorithm when diagnosing CMS in Balkan region: with predominance of postsynaptic CMS in the first place mutation in CHRNE, which should be considered first.

Disclosure: Nothing to disclose

P3258

Long-term follow-up in patients with the Lambert-Eaton myasthenic syndrome

A.F. Lipka[1], M.J. Titulaer[2], J.J. Verschuuren[1]

[1]Leiden, The Netherlands, [2]Erasmus Medical Center, Neurology, Rotterdam, The Netherlands

Background and aims: Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder causing fluctuating muscle weakness and autonomic dysfunction. Symptoms usually progress over the first months. After diagnosis, symptoms can vary between long-lasting remission upon treatment, frequent fluctuations, and permanent disability. Few, small studies have characterized functional impairments of LEMS patients over a longer period of time.

Methods: Disease course in LEMS patients was recorded retrospectively, using a structured interview combined with medical records. We used modified Rankin Scale (mRS) and Karnofsky performance scales (KPS) to grade functional impairment.

Results: 23 LEMS patients (including 6 with lung cancer) were included, with a median follow-up of 63 months (range 3 months – 29 years). 2 patients died 16 and 20 months after onset because of lung cancer. 21 patients (91%) reported secondary progression after initial onset, before LEMS was diagnosed. At diagnosis, 8 patients (35%) were dependent for self-care (KPS<70), decreasing to 19% at 1 year afterwards. 16 patients were only treated symptomatically, 7 with immunosuppressive drugs. Distribution of KPS and mRS over the disease course and at maximum severity are detailed in Fig 1 and 2. Exacerbations after diagnosis were present in a minority of 10/23 (43%) patients.

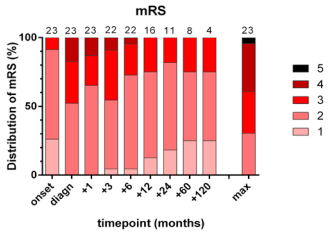


Fig 2. Distribution of modified Rankin Scale (mRS) at onset of symptoms, diagnosis, 1, 3, 6, 12, 24, 60 and 120 months after diagnosis and at maximal disease severity. Number of patients available at top of bar for each timepoint.

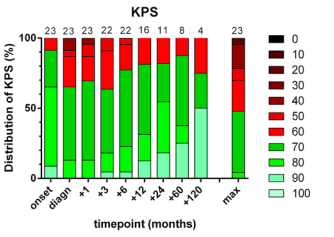


Fig 1. Distribution of Karnofsky Performance Scale (KPS) at onset of symptoms, diagnosis, 1, 3, 6, 12, 24, 60 and 120 months after diagnosis and at maximal disease severity. Number of patients available at top of bar for each timepoint.

Conclusion: A majority of LEMS patients in our study report a stable disease course after diagnosis and treatment. Most patients either remain or become independent for self-care over time, after appropriate treatment.

Disclosure: Nothing to disclose

P3259

Malonyl-CoA inhibits not only carnitine palmitoyltransferase II but even more pronounced the S113L variant of this enzyme

L. Motlagh[1], R. Golbik[2], W. Sippl[3], S. Zierz[4]
[1]Halle, Germany, [2]Martin Luther University Halle-Wittenberg, Institute of Biochemistry and Biotechnology, Halle, Germany, [3]Martin Luther University Halle-Wittenberg, Institute of Pharmacy, Halle, Germany, [4]Martin Luther University Halle-Wittenberg, Department of Neurology, Halle, Germany

Background and aims: It is still the prevailing view that only carnitine palmitoyltransferase (CPT) I but not CPT II is inhibited by malonyl-CoA. The almost complete inhibition of total CPT activity (i.e. CPT I and CPT II) by malonyl-CoA in muscle homogenates from patients with CPT II deficiency has been interpreted either as a lack of an active enzyme or an abnormal sensitivity of the mutated CPT II to malonyl-CoA. Muscle CPT II deficiency is the most common defect of lipid metabolism in skeletal muscle. In about 90% of patients the underlying defect is a S113L mutation in the CPT II gene.

Methods: Recombinant His6-N-hCPT2 and His6-N-hCPT2/S113L were produced and characterized according to their functional and regulatory properties. A model of malonyl-CoA binding to wild type and mutated CPT II is suggested by docking studies.

Results: The wild type and its variant S113L showed the same enzymatic activity. Both enzymes were inhibited by malonyl-CoA. This inhibition was, however, significantly more pronounced for the mutated enzyme.

The mutated enzyme revealed an abnormal thermal destabilization at 40°C. This temperature might simulate the fever situation, which is known to provoke attacks of myoglobinuria in CPT II-deficient patients.

Conclusion: Thus, the problems of CPT II-deficient patients are not due to a loss of catalytically active enzyme but rather might be due to the impaired thermal stability and an abnormal regulation.

These results clearly indicate that CPT II can also be inhibited by malonyl-CoA. This inhibition is, however, significantly more pronounced in CPT II-deficient patients.

Disclosure: Nothing to disclose

Neurorehabilitation; neuro-traumatology

P3260

Longitudinal white matter alteration in patients with moderate to severe consciousness disorder due to traffic accident-related brain injury

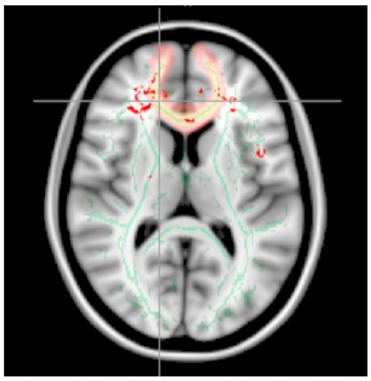
H. Abe[1], K. Shimoji[2], T. Kondo[3], T. Kochiyama[4], T. Chiba[5], Y. Nagamine[6], S. Fujiwara[7], Y. Oouchida[8], S.-I. Izumi[9]

[1]Kohnan Hospital Tohoku Ryogo center, Department of Rehabilitation Medicine, Sendai, Japan, [2]Tokyo Metropolitan Geriatric Hospital, Department of Diagnostic Radiology, Tokyo, Japan, [3]Graduate School of Medicine, Tohoku University, Department of Physical Medicine and Rehabilitation, Sendai, Japan, [4]Brain Activity Imaging Center, Advanced Telecommunications Research Institute, Kyoto, Japan, [5]Kohnan Hospital, Department of Radiology, Sendai, Japan, [6]Kohnan Hospital Tohoku Ryogo center, Department of Neurosurgery, Sendai, Japan, [7]Kohnan Hospital, Department of Nerurosugery, Sendai, Japan, [8] Graduate School of Medicine, Tohoku University, Department of Physical Medicine and Rehabilitation, Sendai, Japan, [9]Graduate School of Biomedical Engineering, Tohoku University, Department of Physical Medicine and Rehabilitation, Sendai, Japan

Background and aims: We analysed the longitudinal white matter (WM) alteration using whole brain and regional brain diffusion tensor imaging analysis in patients with consciousness disorder (CD). Furthermore, we investigated whether WM alteration was correlated with the degree of CD.

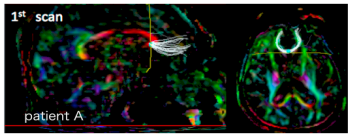
Methods: 7 patients with CD due to traffic accident-related brain injury underwent diffusion tensor imaging with a 3T magnetic resonance imaging. First and second scans were performed at 135–400 days and 288–849 days after insults, respectively. The severity of CD was measured using the Kohnan score, which measures the recovery from severe persistent vegetative state. We analysed the fractional anisotropy (FA) value using the tract-based spatial statistics technique (whole-brain analysis). We subsequently focused on measuring the mean FA value of the forceps minor (FM) of all subjects by tract-specific analysis (regional brain analysis). We used Pearson correlation coefficients to evaluate the relationship between FA value and the degree of improvement from CD.

Results: In the whole-brain analysis, FA values significantly decreased in part of FM at second scan $p<0.05$, family-wise error corrected). Further, in the regional brain analysis, mean FA value significantly decreased at second scan (0.57±0.4 at first, 0.53±0.3 at second scan). A significant positive correlation was observed between the improving CD and the number of voxels with a FA value >0.5 in whole brain ($r=0.78$, $P<0.05$).

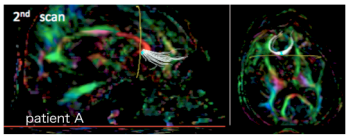


FA values significantly decreased in part of FM at second scan ($p < 0.05$, family-wise error corrected)

Result of TBSS(tract-based spatial statistics technique)



Results of TSA(tract-specific analysis) at first scan (one patient).



Result of TSA at second scan (one patient)

Conclusion: Our results show that microstructural WM changes occur in patients with CD. FA values may be useful indices of WM alterations in patients with CD.

Disclosure: This study was supported by a medical research grant on traffic accident from the General Insurance Association of Japan. This study is supported by a Grant-in-Aid for scientific research in innovative areas (Comprehensive Brain Science Network) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

P3261

Abstract cancelled

P3262

Abstract cancelled

P3263

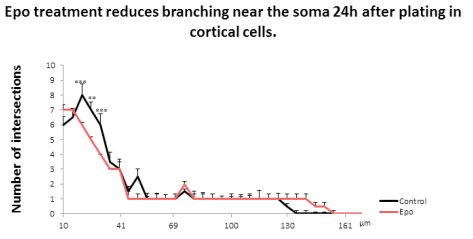
Promotion of axonal collateral branching as potential mechanism underlying erythropoietin-induced poststroke plasticity

D.M. Hermann, E. Sanchez
Essen, Germany

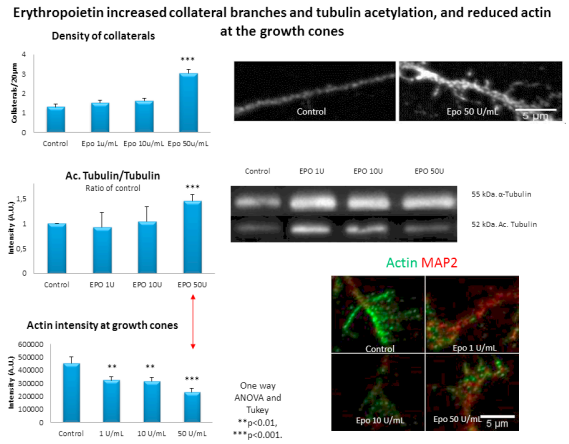
Background and aims: We have previously demonstrated that erythropoietin (Epo) induces contralesional pyramidal plasticity after transient middle cerebral artery occlusion (t-MCAO), thereby enhancing neurological recovery.

Methods: To elucidate mechanisms underlying this process we exposed embryonic cortical neurons to increasing concentrations of Epo for 24h during the polarization phase in vitro.

Results: Contrary to what was expected, we found that high concentrations of Epo (50 I.U./mL) did not change the length of the axon but reduced the number of branches at 20 µm from the soma as measured by Scholl analysis (8.0±1.5 (control) vs. 6.0±0.5 (Epo treated); P<0.01). However the density of small collateral sprouts was significantly increased when compared to control (1.3±1.3 (control) vs 3.0±1.7 (Epo treated) collaterals/ 20µm; P<0.001). Interestingly, this increase in collateral branching was accompanied by an overall increase in the ratio of tubulin acetylation (+50% in Epo treated; P<0.001) and a decrease of actin signal (-50% in Epo treated; P<0.001) at the tip of the growth cone.



Scholl analysis was performed to evaluate ramification of cortical cells. This procedure revealed a significant reduction in the median value of intersections at the distance between 20 and 25µm from the center of the soma. **p=0.013, ***p<0.01.



Conclusion: The balance of tyrosylated and acetylated tubulin determines the dynamics of polymerization of microtubuli. High levels of tyrosylated tubulin are necessary for axonal growth whereas acetylated tubulin is a more stable form of tubulin which enhances the mobility of kinesin-1 and axonal specification. Our data provide important insight into how Epo influences brain plasticity poststroke, identifying axonal collateral formation as potential therapeutic target.

Disclosure: Nothing to disclose

P3264

Simple prognostic scale for traumatic brain injury patients: 5-year prospective population study

A. Korchut, S. Szklener, K. Rejdak
Lublin, Poland

Background and aims: Traumatic brain injury (TBI) is a major global public health issue so that searching for new prognostic tools can be useful to create optimal strategy for neuroprotection of patients after TBI. We focused on developing of prognostic scale based on admission characteristics which would allow for application of the model before in-hospital therapeutic interventions.

Methods: In this paper we present the prognostic value of factors on admission after TBI by using univariate and multivariable analysis. The test group comprised of 208 patients after TBI (24 excluded from the study) who were admitted to Neurology Department of Lublin Medical University. In the tested group were patients with full recovery outcome and unfavorable outcome, based on the Glasgow Outcome Scale (GOS) at 6 months after injury.

Results: The independent factors on admission after TBI include: age, Glasgow Coma Scale (GCS), systolic blood pressure (SBP), Marshall CT classification. The four categories create simple prognostic scale in TBI. The scale provides a score in the range from 0 to 6 points. Patients with a score ≤ 2 achieved usually full recovery and with a score >2 points were assessed as unfavorable outcome. The scale as a prognostic background to assess full recovery of patients after TBI is characterised by high sensitivity 97.22% and specificity 75.00%, positive predictive value 93.30% and negative predictive value 88.20%. Youden index for the scale was 0.7222.

Conclusion: Prognostic Scale in TBI could be a useful clinical tool for easy and fast assessing of patients after traumatic brain injury.

Disclosure: Nothing to disclose

P3265

An exploratory intervention study suggests clinical benefits of training in chronic stroke to be paralleled by changes in brain activity using repeated fMRI

B. Landsmann[1], D. Pinter[1], E. Pirker[1], E. Wallack[2], G. Pichler[2], W. Schippinger[3], S. Ropele[1], T. Gattringer[1], F. Fazekas[1], C. Enzinger[1]
[1]Medical University of Graz, Neurology, Graz, Austria, [2]Albert Schweitzer Clinic Graz, Neurology, Graz, Austria, [3]Albert Schweitzer Clinic Graz, Internal Medicine, Graz, Austria

Background and aims: Previous studies demonstrated changes in sensorimotor network activation after stroke that have been interpreted as partly compensatory. Mobility trainings may improve both mobility and cognition and normalise cerebral activation. We here aimed to test these assumptions in an exploratory study to inform future larger intervention studies.

Methods: 8 patients (73.3±4.4 yrs) with chronic (mean interval 3.7 yrs) ischemic hemispheric stroke and residual gait disturbance received a dedicated five week training. Before and afterwards, they underwent neuropsychological and gait assessments and MRI of the brain at 3T including a functional ankle movement paradigm. 16 healthy controls (HC; 68.8±5.4 yrs) followed the same protocol without intervention.

Results: After training, patients showed improved mobility, memory and partly processing speed. While cerebral activations in HC remained constant, at baseline, patients compared to HC demonstrated increased activation in the contralesional precuneus and pre- and postcentral gyri with movement of the right foot. After training, these differences disappeared, suggesting a normalisation of brain activation in the patients.

Conclusion: The present study documents the feasibility of a complex study including repeated MRI and outpatient rehabilitation through close collaboration. These preliminary data also suggest that a training intervention focussing on mobility, endurance and coordination may improve cognition and induce neuronal plasticity. Future studies need to test the specificity and sustainability of these findings.

Disclosure: Our study has been granted by Land Steiermark.

P3266

Neurorehabiliation outcome in hypoglycaemic encephalopathy: a case series

K. Lange, W. Nager, E. Walther
Schön Clinic Hamburg Eilbek, Neurocentre, Neurology and neurological rehabilitation, Hamburg, Germany

Background and aims: Hypoglycaemic encephalopathy (HE) can be defined as an unique metabolic brain insult [Auer, 2004], which presents as coma/stupor and blood glucose levels <50mg/dl on admission, persistence of coma/stupor for ≥24h despite normalization of blood glucose levels, and exclusion of any other cause of coma/stupor [Witsch et al., 2012]. Data on the clinical rehabilitation outcome after the acute phase of HE is currently very limited.

Methods: Retrospective case study: patients admitted between January 2010 and April 2014 with principal or secondary diagnosis G93 ('Other disorders of brain'). Data of patients with confirmed HE (apparative diagnostics; physio-, ergotherapeutical, logopedical and neuropsychological records) were examined.

Results: Of all 311 patients with G93, 5 (1 male, 4 female) matched with the diagnosis of HE. The mean age was 44 years (range 35-64 y.), mean initial blood glucose level 14,2 mg/dl. Diabetes mellitus was known in one patient, four had attempted suicide.

The mean duration of phase B neurorehabilitation was 106 days (range 46-177 d.). One patient was dismissed in minimally conscious state. All 4 post-suicidal patients achieved alertness with relatively well preserved motor abilities whereas psychomotor agitation, disorientation and distinct cognitive restrictions remained.

The patient with poor outcome showed no cortical response in sensible evoked potentials. We found no additional relations between cCT/cMRT, EEG and clinical outcome.

Conclusion: In 4 of 5 patients we saw distinct cognitive impairments by well preserved motor abilities after the multimodal neurorehabilitation. This demonstrates the necessity for further, directed studies.

Disclosure: Nothing to disclose

P3267

Controlled clinical trial of repeated left prefrontal tDCS in patients with chronic minimally conscious state

C. Martial[1], A. Thibaut[1], M.-A. Bruno[1], S. Wannez[1], C. Chatelle[2], D. Anne-Françoise[3], P. Maquet[4], S. Laureys[1]
[1]ULg, Cyclotron Research Centre, [2]Harvard Medical School, Rehabilitation Hospital, [3]University of Liège, Biostatistics Department, [4]University of Liège, Cyclotron Research Centre, University Hospital of Liège, Liege, Belgium

Background and aims: A recent study showed that single-session anodal transcranial direct current stimulation (tDCS) applied to the left dorsolateral prefrontal cortex (LDLPF) transiently improves consciousness in 43% of patients in minimally conscious state (MCS) (1). We here test the potential effects and safety of repeated tDCS in severely brain-damaged patients with MCS. 1. Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. Neurology. 2014 Apr 1;82(13): p. 1112-8.

Methods: In this double-blind cross-over sham-controlled experimental design, we delivered two sessions of repeated (5 days of stimulation) tDCS, either anodal or sham in a randomized order. We stimulated the LDLPF cortex (Figure1) during twenty minutes in 20 MCS patients (12men, 48±16 years, time since onset 78±95 months, 12 post-traumatic). Consciousness was assessed by the French adaptation of the Coma Recovery Scale Revised (CRS-R) before and after each stimulation (Figure2).

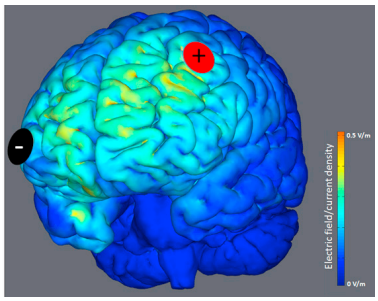


Fig. 1 Left Dorsolateral Prefrontal Cortex (LDLPF)

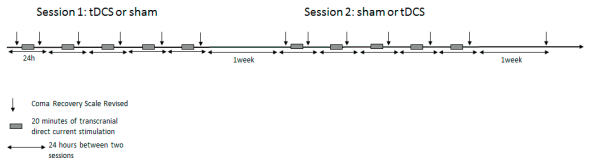


Fig. 2 Protocol

Results: A treatment effect was observed for the comparison between CRS-R total scores at baseline and after 5 days of real tDCS ($p<0.01$). Behaviorally, 10/20 patients showed a tDCS-related improvement; 5 patients responded after the first stimulation and 5 other patients responded after 2, 3 or 4 days of stimulation (Figure3). No side effect (e.g. epilepsy) was reported.

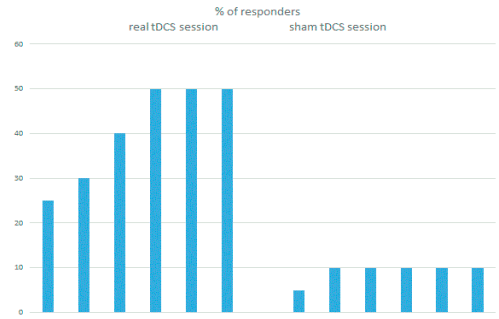


Fig. 3 Graphique

Conclusion: Our results demonstrate that repeated (5 days) anodal LDLPF tDCS is safe and might improve signs of consciousness in about half of patients in MCS. It is important to note that the first session is not predictive for a future positive effect of the efficacy of the non-invasive electrical stimulation.
Disclosure: Nothing to disclose

P3268

Fatigue after traumatic brain injury

B. Carlan[1], M. Moarcas[2], R. Mircea[3], A. Voina[3], S. Paripas[3], S. Diaconu[4], C. Falup Pecurariu[4]
[1]Faculty of Medicine, Transilvania University Brasov, Brasov, Romania, [2]Emergency County Hospital Brasov, Neurology, Brasov, Romania, [3]Emergency County Hospital Brasov, Neurosurgery, Brasov, Romania, [4]Brasov, Romania

Background: Fatigue may appear as a consequence of traumatic brain injury (TBI). It can interfere with daily life functioning, duties at work and can also alter quality of life. It is subjectively defined, but can be assesed with specific scales.
Objectives: To evaluate the prevalence of fatigue among patients with traumatic brain injury and the impact of this symptom on general quality of life.
Methods: We conducted a prospective study on 41 patients with mild and moderate TBI in a period of 6 months. The instruments we used to evaluate fatigue were Fatigue Symptom Inventory (FSI) and Fatigue Severity Scale (FSS).
Results: The study group included 28 men (68.29%), with a mean age of 43.5±17.26 years. Following traumatic brain injury, 69.69% of the patients experienced fatigue, of which 27%, reported very severe and 17% severe symptoms. 19.51% of patients totally agreed that fatigue is among their three most disabling symptoms and has a negative impact on their work, family or social life. Less than a quarter of the patients identified physical activity as a cause of their fatigue.
Conclusion: Fatigue is a frequent symptom reported by patients with traumatic brain injury. It impacts the quality of life and standardized methods aid the clinician in identifying it.
Disclosure: Nothing to disclose

P3269

Characteristics of focused and sustained attention and EEG of soccer players with recurring mild head injuries

P. Radić[1], B. Radić[2], M. Mišigoj-Duraković[3], D. Vukleta[3], D. Milanović[3]

[1]University of Zagreb, School of Medicine, Zagreb, Croatia, [2]University Hospital Center Zagreb, Department of Neurology, Zagreb, Croatia, [3]University of Zagreb, Faculty of Kinesiology, Zagreb, Croatia

Background and aims: The soccer players with head injury contribution ranging from 4 to 22%. Attentional and cerebral electrical activity impairments as the consequences of mild recurring traumatic brain injury (TBI) caused by heading the ball and blows to the head.

Methods: The study included the experimental sample of 70 male amateur soccer players, competing in a veteran league, with previous senior competition experience, and 70 control subjects with no soccer experience. Cognitive tests were applied on the groups as well as EEG recordings together with spectral analysis.

Results: Comparison between the groups revealed significant attention deficits in experimental group (EG) in the tasks requiring simple reaction time (SRT) and attention sustained through a longer time interval. Soccer playing experience affected all the tests' scores except for the decision response time (DRT). In EG certain EEG changes were found in the frontotemporal region

Conclusion: The findings of the research that compared the group of soccer players and the controls indicate significant attention deficits in footballers when they were performing tasks requiring simple reaction and attention maintenance over a longer time interval. In the group of footballers EEG changes were found in the cerebral frontotemporal region. The found EEG changes can be related to the existent cognitive deficits, but they are not cognitive disorder specific on their own.

Disclosure: Nothing to disclose

P3270

Barriers to recovery from concussion

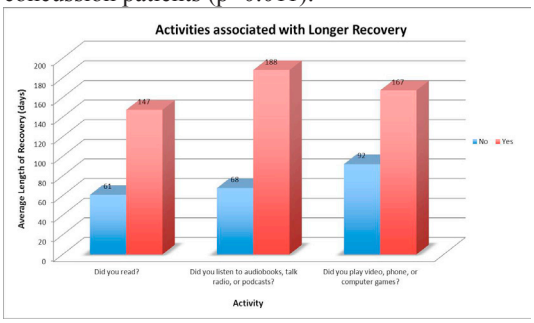
T. Shetty[1], K. Cummings[1], K. Halvorsen[2], M. Singer[3], J. Nguyen[4]

[1]Hospital for Special Surgery, Neurology , New York, USA, [2]Williams College, Williamstown, USA, [3]Princeton University, Princeton, USA, [4]Hospital for Special Surgery, Biostatistics Core, New York, USA

Background and aims: The prescribed treatment for concussion is physical and cognitive rest. Physicians and patients struggle with defining the prescription of 'rest' and understanding the consequences of compliance. This study attempts to determine factors influencing recovery from a concussion and investigate the correlation between duration and quality of rest and recovery time.

Methods: Patients between the ages 10 and 50 years seen for a concussion were asked to complete a questionnaire regarding their activity during their recovery period. A total of 220 patients were asked to participate from November 2011- May 2014 and 45 completed it by this time.

Results: On average, females had a longer recovery time compared to males (116 verses 97 days, respectively). Alcohol ($p=0.126$), cigarette ($p=0.037$), and marijuana ($p=0.003$) consumers/users had a far greater recovery time. While many activities were associated with longer recovery times, only reading ($p=0.028$) and listening to audio books/talk-radio/podcasts ($p<0.001$) were statistically significant. Patients who played video/phone/computer games had nearly double the recovery time compared to those who did not play those games. Patients who had previous concussions had a recovery length 3.5 times longer than first time concussion patients ($p=0.011$).



Participates who answered "yes" to questions regarding reading, listening to audio books, talk radio, or podcasts, or playing video, phone, or computer games, had longer recoveries than those who answered "no".

Conclusion: Gender, pastimes, alcohol and substance consumption during recovery, and prior concussion history have a significant impact on recovery time. Females have a more difficult time recovering than males and suffer symptoms for greater lengths of time. Simple activities, such as reading or audiobooks, may in fact impede recovery. A history of multiple concussions poses greater challenges during recovery.

Disclosure: Dr. Shetty has a grant from GE and the NFL to research imaging in mild traumatic brain injury. This is a separate research project from the abstract above.

Peripheral nerve disorders 3

P3271

Autosomal Recessive Charcot-Marie-Tooth disease: Clinical, electrophysiological and genetic spectrum in a Tunisian series

I. Kacem[1], A. Nasri[1], Y. Sidhom[1], L. Sellami[1], Y. Hizem[1], M. Ben Djebara[1], A. Gargouri[1], E. Leguern[2], R. Gouider[1]
[1]Razi Hospital, Tunis, Department of Neurology/ Research Unit UR12SP21, Tunis, Tunisia, [2]La Pitié Salpêtrière Hospital, Department of Genetics and Cytogenetics, Paris, France

Background and aims: Autosomal Recessive Charcot-Marie-Tooth (AR-CMT) disease is a genetically heterogeneous group of hereditary neuropathies. It is considered as a rare form of CMT in European countries. Our goal is to report clinical, electrophysiological and genetic characteristics of a Tunisian AR- CMT series.

Methods: We performed a prospective study of a cohort of AR-CMT Tunisian patients followed in the neurology department of Razi Hospital, Tunisia from 2002 to September 2014. Clinical and electrophysiological data were analyzed. Genetic screening, including most of the known genes involved in this form of disease, was performed and analyzed.

Results: Among 100 patients with CMT, we included 39 patients belonging to19 families. Consanguinity was found in 94% of families. Mean age of onset was 4.2 years, mean Over Neuropathy limitations Scale (ONLS) was 4.7; mean Charcot Marie Tooth Neuropathy Score (CMTNS) of 20. Electrophysiological data showed demyelinating forms in 51.5% and axonal ones in 48.5%. These later were associated to an early onset (90.9%) ($p<0.001$), and a severe ONLS score ($p=0.04$). Molecular diagnosis was performed in all families; gene mutations were identified in 08 families. The mutations in the GDAP1 gene were the most frequent (50%), followed by MPZ gene (25%).Four novel mutations were detected and characterized phenotypically.

Conclusion: ARCMT are more frequent in our country because of high consanguinity rate. They are characterized by an early onset with a severe phenotype. GDAP1 gene mutations still the most frequent mutation in these cases.

Disclosure: Nothing to disclose

P3272

Hypereosinophilia and vasculitic neuropathy without lung manifestation. An atypical presentation of Churg-Strauss syndrome.

A. Grisold[1], C. Weber[1], H. Kiener[2], G. Kovacs[3], P. Schnider[4], E. Auff[1], F. Zimprich[1]
[1]Medical University of Vienna, Department of Neurology, Vienna, Austria, [2]Medical University of Vienna, Department of Internal Medicine, Vienna, Austria, [3]Medical University of Vienna, Clinical Institute of Neurology, Vienna, Austria, [4]Landesklinikum Hochegg, Department of Neurology, Hochegg, Austria

Background and aims: Churg-Strauss syndrome (CSS) is a rare form of eosinophilic vasculitis associated with asthma. In 20 to 50% peripheral neuropathies occur and may be the initial manifestation. The neuropathy is often asymmetric, presenting as mononeuritis multiplex. CNS involvement is rare. Systemic organ manifestation is frequent. Hypereosinophilia and elevated p-ANCA are indicative. In NCV an asymmetric distribution of axonal neuropathy is found, EMG shows denervation depending on the stage of the disease. Nerve biopsies show necrotizing vasculitis or microvasculitis with perivascular infiltrates. Treatment consists of corticosteroids or cyclophosphamide.

Results: A 71-year old male patient presented with backpain followed by paraesthesias in all extremities. Within 3 weeks he developed an asymmetric quadriparesis, accentuated in the legs. Initially a Guillain-Barré syndrome was suspected and the patient received intravenous immunoglobulins with only minor and temporary improvement. In the course of further evaluations a striking eosinophilia, elevated P-ANCA titers and CRP in combination with the findings of an asymmetric axonal neuropathy (mononeuritis multiplex) suggested a CSS, though in the absence of typical lung lesions and without clinical evidence of asthma the diagnostic criteria were not fully met. Nerve biopsy showed an axonal neuropathy with microvasculitic changes, but no evidence of necrotizing vasculitis. The patient responded well to steroids, followed by cyclophosphamide. Subsequently strength and mobility improved and sensory symptoms and pain diminished.

Conclusion: The combination of mononeuritis multiplex with hypereosinophilia is very suggestive of CSS. Despite the criteria were not completed, a therapeutic trial with steroids is warranted as this case demonstrates.

Disclosure: Nothing to disclose

P3273

Small fiber neuropathy associated with copper deficiency

M.J. Ibanez, M. Frasquet Carrera, R. Vílchez, N. Muelas, T. Sevilla, J.J. Vilchez
Valencia, Spain

Background and aims: Copper deficiency is a rare cause of myelopathy mimicking vitamin B12 deficiency subacute combined degeneration. Neuropathy has been less frequently described as an axonal large fiber neuropathy. To our knowledge, no cases of small fiber neuropathy due to copper deficiency have been reported.

Methods: We report a retrospective series of 8 patients with copper deficiency and clinical evidence of small or mixed fiber neuropathy. Skin biopsy samples were taken at distal leg and proximal thigh levels and were analysed with bright-field immunohistochemistry protocol and quantification of intraepidermal nerve fiber (IENF) density. Six muscle biopsies were also analysed by conventional histological and histochemical techniques.

Results: 5 patients showed copper deficiency and three other presented with both copper and B12 deficiency. 5 patients expressed a mixed large and small fiber neuropathy profile while the other three subjects only had clinical evidence of small fiber neuropathy with no large fiber involvement in electrophysiological studies. Half of the patient series combined myelopathic features with impaired somatosensory evoked potentials and normal spinal magnetic resonance imaging (MRI) Low distal IENF density and less pronounced proximal INF depletion was observed in all patients suggesting a length dependent small fiber neuropathy. Many muscle fibres showed absent or reduced COX staining. After copper supplementation myelopathic symptoms remain stable but dysesthesia and pain have improved considerably in all cases.

Conclusion: Copper deficiency is a rare cause of small fiber neuropathy and it should be included in the differential diagnosis. Additionally, copper supplementation may stabilize or even improves the clinical symptoms.

Disclosure: Nothing to disclose

P3274

Chronic inflammatory demyelinating polyneuropathy (CIDP) sera reduce the ability of Schwann cells to support axonal regeneration

A. Joshi, I. Bobylev, H.C. Lehmann
University Hospital of Cologne, Neurology, Cologne, Germany

Aims: To explore the role of Schwann cell (SC) regulators in the pathogenesis of CIDP.

Background: Despite immunosuppressive treatment, a significant proportion of CIDP patients experiences progressive impairment or incomplete improvement after a relapse, which can be attributed to the degree of axonal injury and incomplete regeneration. After nerve injury SC usually proliferate and dedifferentiate from a myelinating to an axon growth supporting non-myelinating phenotype. This phenotypic switch is controlled by a set of transcription factors including c-Jun and p57kip2. We hypothesized that inflammatory mediators could alter transcriptional program and diminish the pro-regenerative function of Schwann cells in CIDP which may account for the axonal loss.

Methods: In an in vivo model of delayed nerve repair we explored the effects of transplanted SCs treated with various control and CIDP sera. In vitro, SC cultures were treated with sera from CIDP patients or non-inflammatory disease controls (NIC).

Results: After chronic denervation, transplanted SCs treated with CIDP sera were much less supportive for axonal regeneration than those exposed to controls. In vitro, treatment with CIDP sera significantly decreased the expression of c-Jun and p57kip2 and significantly altered SC morphology. IgG fractions from CIDP patients did not induce any morphological changes. A comparative cytokine array revealed that CIDP sera contained significantly less granulocyte monocyte colony stimulating factor (GM-CSF) compared to control sera.

Conclusion: Our data implicate that the altered inflammatory cytokine network in CIDP influences regulators of SC differentiation, which results in suboptimal support of SC for axonal regeneration.

Disclosure: Nothing to disclose

P3275

Tafamidis reduces disease progression in patients with transthyretin familial amyloid polyneuropathy: supportive post-hoc analyses of a pivotal trial

D. Keohane[1], J. Schwartz[1], B. Gundapaneni[2], M. Stewart[1], L. Amass[1]

[1]Pfizer Inc., NY, USA, [2]Inventiv Health, MA, USA

Background and aims: Safety and efficacy of once-daily 20 mg tafamidis, a transthyretin (TTR) stabilizer, was evaluated in an 18-month, multicenter, randomized, double-blind, placebo-controlled study in 128 patients with early symptomatic V30M TTR familial amyloid polyneuropathy (TTR-FAP). In the intent-to-treat population, a responder analysis for Neuropathy Impairment Score-Lower Limb (NIS-LL) (co-primary with Norfolk Quality of Life-Diabetic Neuropathy) favored tafamidis (p=0.07). A prespecified, key secondary analysis of change from baseline to Month 18 in NIS-LL continuous scores was significant (p=0.04). Additional post-hoc analyses supporting tafamidis for delaying progression of TTR-FAP are reported here.

Methods: Change from baseline in NIS-LL over time was analyzed with the addition of baseline as a covariate in a repeated measures model. A sensitivity multiple imputation analysis with imputed values based on assigned treatment group was also performed. Additionally, change in NIS-LL+Σ7 (neurophysiological function composite endpoint) over time was assessed.

Results: When adjusted for baseline NIS-LL disease severity, statistical significance in change from baseline to Month 18 NIS-LL was retained. The magnitude of separation between placebo and tafamidis was consistent across the full range of baseline values (Figure 1). Treatment effect estimates from the multiple imputation analysis, although reduced, were similar to those from the analysis of change from baseline to Month 18 as a continuous variable, and remained significant (Table 1). Significant differences between treatment groups were observed for NIS-LL+Σ7 at Months 12 and 18 (Figure 2).

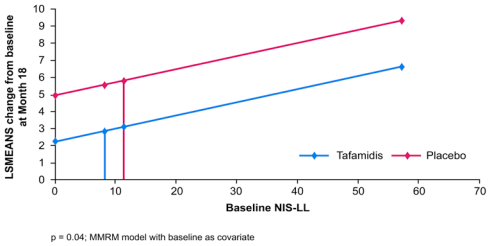


Figure 1. Baseline-adjusted change from baseline in NIS-LL at month 18

Table 1. Imputation results for NIS-LL change from baseline to Month 18 analysis

Multiple Imputation Batch Run*	Change from Baseline Difference for Tafamidis vs. Placebo	Standard Error	Confidence Interval	P-value
1	-2.787	1.345	-5.423, -0.151	0.04
2	-2.815	1.351	-5.464, -0.166	0.04
3	-2.798	1.347	-5.438, -0.157	0.04

*Each batch run represents the results combined from 1000 multiply imputed data sets.

Table 1. Imputation results for NIS-LL change from baseline to month 18 analysis

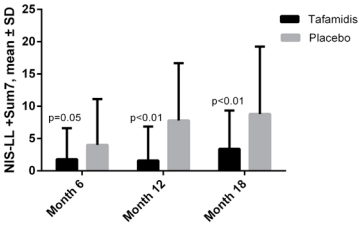


Figure 2. NIS-LL +Σ7 change from baseline at months 6, 12, and 18

Conclusion: The beneficial effects of tafamidis in delaying neurological impairment in TTR-FAP are further supported by these post-hoc analyses.

Disclosure: This study was funded by Pfizer Inc.

P3276

Validation of mEGOS score as a predictor of outcome among Guillain Barré syndrome patients in Thailand

K. Kulkantrakorn, P. Sukphulloprat
Thammasat University, Internal Medicine, Pathumthani, Thailand

Background and aims: Survivors from Guillain Barré syndrome (GBS) often had longterm disability. Data about prognostic factors are sparse in Thailand. The objective of this study is to validate the well recognized clinical prognostic scoring system, modified Erasmus outcome score (mEGOS) among GBS patients in Thailand.

Methods: Retrospective study of GBS patients who were at least 15 years old, admitted to Thammasat University Hospital and Bangkok Hospital between 1st January 2009 and 30th November 2014. Correlation and regression analysis between mEGOS at admission and severe motor disability at last follow up was performed.

Results: 30 patients were recruited. Demographic data are as follows; 60% male; average age 54 years; Asian 60%, European 20%, others 10%. Clinical subtypes are classic GBS 83.3%, PCB 3.3%, acute pharyngeal weakness 3.3%, bifacial weakness with paresthesia 3.3%, classic MFS 3.3%, acute opthalmoparesis 3.3%. Average GBS disability score at admission was 2.9. Immunotherapy was IVIg 83.3%, plasma exchange 3.3%, steroid 3.3%. Average length of stay was 14.2 days, assisted ventilation rate was 13.3%. After one-year follow-up, average GBS disability score was 2, good outcome (score <3) was 63.3% and no death. Significant correlation between mEGOS and severe motor disability was observed (correlation coefficient 0.409, p-value 0.025). Optimal cut-off value for mEGOS was estimated by logistic regression analysis to be 4 (AUC 0.72)

Conclusion: mEGOS has a good performance for prediction of severe motor disability among GBS patients in Thailand

Disclosure: Nothing to disclose

P3277

Carpal tunnel neuropathy: a study of 1600 successive cases according to gender, age and severity

P. Lebrun-Grandie[1], L. Letenneur[2]
[1]Périgieux, France, [2]INSERM U897, ISPED case 11, 146 rue Léo Saignat, 33076 Bordeaux Cedex, Bordeaux, France

Background and aims: The Carpal Tunnel Syndrome (CTS) is the most frequent focal neuropathy. Diagnosing a CTS is a clinical approach and ENMG performs a carpal tunnel neuropathy (CTN) diagnosis. We developed a CTN electrodiagnosis (EDX) approach presented at the AAN 2010 that gives a semi-quantitative estimation with the measurement of the potential amplitude and of the muscle denervation. The objective is to describe the severity of CTN according to age and gender.

Methods: Patients were recruited in private practice, consecutively included in 2009-2014 when EDX of CTN identified incident cases. Paresthesias associated with radiculopathy, arthropathy or other origin were excluded. Severity of CTN is the critical point for surgical decision and was evaluated in 2 levels according to the sensitive amplitude of the median nerve.

Results: Of the 1600 patients, 1117 (70%) were women. Severe CTN was observed in 740 subjects (46.2%). Men showed more severe CTN than women (55% vs 42%). Severity increased with age: in men, 63% had severe CTN at 55-75 years and 89% after age 75. In women, it was 45% and 85% respectively.

Conclusion: The diagnostic of CTN, more than CTS, and the definition of a severe stage is a key for the decision of surgery treatment. Severe CTN occurs frequently in patients examined in a private doctor setting and is more prevalent in men. Severe CTN increases with age and appears early in men.

Disclosure: Nothing to disclose

P3278

Defining central nervous system involvement in patients with acquired demyelinating peripheral neuropathies

L. Vacchi[1], M.A. Rocca[1], N. Riva[2], R. Fazio[3], E. Pagani[1], M. Comola[3], A. Falini[4], G. Comi[3], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Hospital, Milan, Italy, [3]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [4]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: Polyneuropathies (PNP) include heterogeneous conditions in term of aetiology, clinical presentation, prognosis and treatment. We explored the presence and distribution of brain white matter (WM) and gray matter (GM) structural abnormalities in patients with chronic acquired demyelinating PNP.

Methods: We recruited 16 demyelinating neuropathy associated with IgM antibodies against myelin-associated glycoprotein (antiMAG-PNP), 16 chronic inflammatory demyelinating polyneuropathy (CIDP) patients, and 32 age- and gender-matched healthy controls (HC). Voxel-wise methods were used to define the regional distribution of damage in the brain GM and WM.

Results: Compared to HC, both PNP groups had increased right cerebellar volume. CIDP patients had significant atrophy of the left middle-inferior temporal gyrus and left inferior frontal gyrus. Moreover, a distributed pattern of WM atrophy and reduced fractional anisotropy (FA) was detected, involving the bilateral corona radiata, corpus callosum, external capsule, cingulum, left superior longitudinal fasciculum and right internal capsulae. AntiMAG-PNP patients had decreased mean diffusivity (MD) in posterior thalamic radiations and left sagittal stratum, as well as decreased axial diffusivity (AD) in bilateral corona radiata, internal capsule, sagittal stratum, corticospinal tracts, thalamic radiations, left corpus callosum, external capsule and fornix. Similar AD abnormalities were detected in antiMAG vs CIDP patients.

Conclusion: Distributed CNS abnormalities occur in PNP patients. Increased cerebellar volume could be an index of a compensatory mechanism, while WM alterations in CIDP support the occurrence of central myelin involvement. The different behaviour of FA, MD and AD indices may suggests different pathogenetic mechanisms, which may contribute to explain differences in clinical profiles.

Disclosure: Nothing to disclose

Spinal cord and root disorders 2

P3279

A rare cause of cervical myelopathy with cutaneous diagnostic clues

I. McGurgan, R. Lonergan, C. McGuigan
St Vincent's University Hospital, Department of Neurology, Dublin, Ireland

Background and aims: Spinal vascular malformations represent a rare, treatable cause of myelopathy and frequently provide a diagnostic challenge. Spinal dural AVF (DAVF) is the most commonly detected malformation, accounting for 70%. DAVFs originate predominantly in the thoracolumbar spine and typically affect middle-aged men. Reported is a rare case of a DAVF involving the cervical cord diagnosed in a patient with progressive myelopathy and an associated medical condition.

Case Report: A 55-year-old man presented with a three-month history of progressive, bilateral lower limb weakness. Examination demonstrated a spastic paraparesis and multiple cutaneous telangiectasias. Subsequent development of upper limb weakness, acute urinary retention and eventually respiratory compromise resulted in requirement for ventilatory support. MR imaging of spine revealed diffuse T2 hyperintensity in the cervical cord with gadolinium enhancement and cord expansion. Immunomodulatory therapy for a presumed diagnosis of transverse myelitis yielded no response so a vascular aetiology was suspected.

Results: Spinal angiography demonstrated a DAVF involving the upper cervical cord. Endovascular embolisation was successfully performed and a marked clinical improvement was acheived. A clinical diagnosis of hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome [OWR]) was also made and DAVF has been reported as a rare association with OWR.

Conclusion: Cervical DAVFs can cause progressive myelopathy, radiculopathy, brainstem dysfunction and subarachnoid haemorrhage. Management typically comprises either endovascular embolisation or surgical interruption. A clinical association with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) was made in this case, and to our knowledge this represents only the second such reported case in the international literature.

Disclosure: Nothing to disclose

P3280

Uncommon extradural lesion causing spinal canal compression – juxtafacet cyst

P. Orosz[1], I. Szőcs[1], G. Varallyay[2], I. Zsigmond[2], G. Rudas[2], D. Bereczki[1], I. Vastagh[1]
[1]Semmelweis University, Department of Neurology, Budapest, Hungary, [2]Semmelweis University, MR Research Center, Budapest, Hungary

Background and aims: Juxtafacet cysts are uncommon degenerative lesions of the joints, they can present with nerve root, myelon and cauda equina compressive syndromes. Lumbar (L) 4 and 5 levels of the spine are most commonly affected, cervical (C) cysts are extremely rare. Several cases of hemorrhage into juxtafacet cysts causing acute symptoms have been reported, but chronic progressive outcome can be present as well. Magnetic resonance (MR) imaging is the first choice diagnostic technique. Surgical resection of the cyst is indicated in case of significant neurologic deficits and pain.

Case Report: We report two cases of chronic progressive synovial cysts resulting in myelon compressive symptoms. A 51-year-old male patient was presenting with cervical and upper back pain. His examination revealed mild spastic paraparesis with left dominance and hypaesthesia distal from thoracal (Th) 10 segment. Cervicothoracal computed tomography (CT) and MR imaging showed a synovial cyst at the CVII and ThI level of the spine. A 46-year-old female patient was complaining about left sided lumbar back pain, paresthesia and weakness of her left foot. Her neurological examination proved palsy of foot extensors and Achilles areflexia on the affected side. Two distinct synovial cysts causing spinal canal stenosis and nerve root compression at the LIV and V segments were detected by lumbar MR imaging.

Results: Cysts were neurosurgically removed, histopathological examinations confirmed the diagnosis of synovial cyst. Post-operatively both patients became pain free and had complete resolution of their symptoms.

Conclusion: The possibility of juxtafacet cysts has to be considered in the differential diagnosis of epidural compressive syndromes.

Disclosure: Nothing to disclose

P3281

Spinal pathology in girls with anorectal malformations

F. Otamurodov, Y.N. Madjidova, N. Ergasheva
Tashkent, Uzbekistan

Background and aims: To study incidence rate and clinical events of the associated disorders of the pelvic organ functions in the girls with anorectal malformations.

Methods and Materials: The investigation included 185 girls with anorectal malformations. The age of patients fluctuated from the first day of life to 15 years. For identification of the accompanying defects of the other organs and systems the patients were performed complex clinical, ultrasound, X-Ray, MSCT (multi-slice computer tomography) and MRI (Magnetic resonance imaging) procedures.

Results: After performance of reconstructive surgeries in spite of good anatomic form in the patients there was noted complication looking-like chronic constipation or incontinence. In these patients were performed MSCT and MRI investigations of the sacrococcygeal area. The associated malformations of the spinal cord were found in 30 patients. Of them in 18 girls there was revealed Spina bifida of the sacrococcygeal site, in 7 – coccygeal agnesia, of them 4 with deformation of the of the sacral vertebrates. The deformation of the spinal cord due to additional vertebrates in the various sites – in 4 patients. Meningocele of the lumbosacral site was found in one patient. As a rule in the malformations of the sacrococcygeal part of the spine the development of the sacral plexus is affected the branches of which innervate the sphincter apparatus of the bladder and rectum that may contribute to decrease in tactile sensitivity of perineum and functional disorders.

Conclusion: Thus, the treatment of associated anomalies of the spinal cord development in children with anorectal anomalies should be performed parallel with team of adjacent specialists.

Disclosure: Nothing to disclose

P3282

Vertebral Artery Dissection (VAD) presenting as a Brown Sequard syndrome: a case report and literature review

S. Qureshi, S. Omer
St George's Hospital, Neurology, London, United Kingdom

Background and aims: We report a case of atraumatic spontaneous vertebral artery dissection in a middle aged lady resulting in cervical cord lesion presenting as Brown Sequard Syndrome. Vertebral artery dissection commonly presents as posterior headache or neck pain accompanied or followed by posterior circulation transient ischemic attack or stroke. Rare clinical features include isolated headache or neck pain, cervical spinal cord ischemia and cervical root impairment. Isolated ischemia of the cervical spinal cord is an uncommon but increasingly recognized complication of vertebral artery dissection (VAD).To the best of our knowledge, this is the fourth case in literature reporting Brown Sequard as a clinical presentation of VAD.

Case Report: A 41-year-old lady of Asian origin working as a part time administrator, presented with right upper arm pain, weakness and tingling in hand with impaired temperature sensations on left side of her body. Eight days before presentation she developed nausea and vertigo of sudden onset in morning. There was no history of trauma, manipulation of neck, preceding headache or neck pain. All potential causes for vertebral artery occlusion were ruled out and we therefore think dissection is the most likely cause.

Conclusion: Vertebral artery dissection is a serious and potentially life-threatening conditon. The diagnosis should be considered in patients presenting with Brown Sequard syndrome as a result of acute cervical spinal cord ischaemia.

Disclosure: Nothing to disclose

P3283

Epidemiology of spinal tuberculosis in a low-incidence Italian region

M. Ricco'
Langhirano, Italy

Background and aims: Spinal tuberculosis (ST) is a destructive form of tuberculosis (TB) with increasing global incidence. Here we present a retrospective database review of reported cases of ST in the Emilia Romagna Region (RER, northern Italy), between 1996 and 2006.

Methods: Data for incident TB cases (1996-2006, n=5,377 cases) in RER were retrieved from a centralized database, focusing on ST (i.e. ICD9=015.0x). Categorical variables were analyzed through chi-square test and logistic regression. Continuous variables were evaluated through Student's t-test/ANOVA.

Results: Notification rate (NR) of TB was 11.4 cases/100,000 inhabitant/year. In total, 97 ST patients (1.8% of total TB cases; M/F=56/41=1.37) were identified, with a NR=0.21 cases/100,000/year. Italian-born people (IBP) were 56 (57.3%): among foreign-born people (FBP), 23 were from AFR-WHO (23.7%) and 11 from EMR-WHO region (11.3%). ST FBP cases were significantly younger than ST IBP and non-ST TB cases (respectively: 32.3±11.07, 58.1±23.66, 51.4±22.37 years; ANOVA p<0.0001). Taking into account IBP as referent group, AFR patients had a significantly higher risk for ST (OR=2.945 IC95%:1.624-5.342). Active TB of other sites was infrequent (Table 1). Alcohol abuse (n=1), diabetes (n=2), HIV+ status (n=1), previous diagnosis of neoplasia (n=5) were not associated with ST diagnosis; also previous history of TB (n=3, 0.57%) was infrequent (non-ST cases=1.98%, p=0.024).

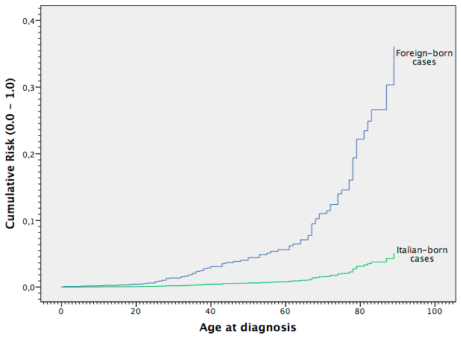


Figure 1. Cumulative risk of ST diagnosis in IBP and FBP. The latter had a higher risk for earlier diagnosis (Cox regression: OR 7.08 95%CI 4.27-11.73).

		N# of ST cases	N# of no-S TB cases	N# of TB cases (tot)	%	chi square test p value
SEX	*Males*	56	3092	3148	1.81%	0.870
	Females	41	2188	2229	1.87%	
Origin	*FBP*	41	1923	1964	2.13%	0.236
	IBP	56	3357	3413	1.67%	
Diagnosis as ...	*inpatient*	6	406	412	1.48%	0.581
	outpatient	91	4874	4965	1.87%	
Diagnosis as ...	*relapse*	5	286	291	1.75%	0.747
	new diagnosis	52	2554	2606	2.04%	
Diagnosis in ...	*previously treated TB*	**3**	**529**	**532**	**0.57%**	**0.024**
	no previous treated TB	**94**	**4751**	**4845**	**1.98%**	
Mantoux Screening test	*positive*	35	1814	1849	1.93%	0.223
	negative	31	2173	2204	1.43%	
Chest X-Ray	*positive*	**30**	**2559**	**2589**	**1.17%**	**< 0.001**
	negative	**27**	**631**	**658**	**4.28%**	
Nutritional status	*malnutrition*	2	121	123	1.65%	0.881
	no malnutrition	95	5159	5254	1.84%	
Neoplasia	*previous diagnosis*	5	300	305	1.67%	0.824
	no diagnosis	92	4980	5072	1.85%	
Diabetes	*positive*	2	229	231	0.87%	0.273
	negative	95	5051	5146	1.88%	
HIV	*positive*	1	179	180	0.56%	0.201
	negative	96	5101	5197	1.88%	
Alcoholism	*positive*	1	62	63	1.61%	0.897
	negative	96	5218	5314	1.84%	
Drug abuse	*positive*	1	46	47	2.17%	0.867
	negative	96	5234	5330	1.83%	
Contact of case	*contact*	2	248	250	0.81%	0.222
	no contact	95	5032	5127	1.89%	
Homeless	*homeless*	11	405	416	2.72%	0.180
	no hameless	86	4875	4961	1.76%	
TB meningitidis	*positive*	0	37	37	0.00%	0.408
	negative	97	5243	5340	1.85%	
Genito-urinary TB	*positive*	**0**	**271**	**271**	**0.00%**	**0.022**
	negative	**97**	**5009**	**5106**	**1.94%**	
Pleural TB	*positive*	1	242	243	0.41%	0.095
	negative	96	5038	5134	1.91%	
Pulmonary TB	*positive*	**12**	**3651**	**3663**	**0.33%**	**< 0.001**
	negative	**85**	**1629**	**1714**	**5.22%**	
Peritoneal TB	*positive*	**0**	**91**	**91**	**0.00%**	**< 0.001**
	negative	**97**	**5189**	**5286**	**1.87%**	
Osteoarticular TB	*positive*	1	66	67	1.52%	0.847
	negative	96	5214	5310	1.84%	
Peripheral LN	*positive*	**1**	**571**	**572**	**0.18%**	**0.002**
	negative	**96**	**4709**	**4805**	**2.04%**	

Table 1. Characteristics of ST patients in confront with non ST TB cases.

		N# of TB cases (tot)	N# of ST cases	%	Ratio	OR§	95%CI LL	95%CI UL	OR#	95%C I LL	95%C UL
Region of origin	**ITA**	3362	56	1.67%	1.000	1.000	-	-	1.000	-	-
	EUR*	379	1	0.26%	0.158	0.159	0.022	1.151	0.143	0.019	1.057
	AFR	424	23	5.42%	3.248	**3.443**	**2.096**	**5.656**	**2.945**	**1.624**	**5.342**
	EMR	724	11	1.52%	0.910	0.926	0.483	1.777	0.789	0.379	1.642
	SEAR	150	2	1.33%	0.798	0.811	0.196	3.356	0.692	0.160	2.988
	WPR	170	4	2.35%	1.409	1.447	0.518	4.037	1.266	0.433	3.797
	AMR	112	0	N.A	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Age Group	**0 - 4**	62	2	3.23%	1.589	1.586	0.374	6.728	1.725	0.398	7.467
	5 - 14	77	4	5.19%	2.559	2.554	0.888	7.346	2.518	0.873	7.263
	15 - 24	417	8	1.92%	0.945	0.943	0.436	2.040	0.946	0.436	2.051
	25 - 44	1819	37	2.03%	1.000	1.000	-	-	1.000	-	-
	45 - 64	978	14	1.43%	0.705	0.704	0.379	1.308	0.759	0.392	1.469
	65 ≥	1927	32	1.66%	0.818	0.816	0.506	1.316	0.953	0.524	1.733

* without ITA cases
§Multinomial Logistic Regression
#Correction for sex

Table 2. ST cases by age groups and geographical origin. Multinomial logistic regression taking in account sex and geophical origin (for age distribution) and age distribution (for geographical origin).

Conclusion: ST is an important public health issue, but remains infrequent in the RER. Its incidence was not significantly influenced by commonly recognized risk factors. Moreover, the typical patient was younger than in previous reports, with a lower prevalence of previously untreated or inadequately treated TB among cases.

Disclosure: Nothing to disclose

P3284

Unilateral calf enlargement: an atypical sign of S1 radiculopathy

T. Santos[1], J. Nunes[2], H. Felgueiras[1], A. Martins-Campos[1], H. Morais[1]

[1]*Centro Hospitalar Vila Nova de Gaia/Espinho, Neurology, Vila Nova de Gaia, Portugal,* [2]*Centro Hospitalar Vila Nova de Gaia/Espinho, Imaging, Vila Nova de Gaia, Portugal*

Background and aims: The approach to unilateral calf enlargement represent a diagnostic challenge, particularly when the diagnosis remain inconclusive after excluding tumoral and vascular etiologies. The cardinal signs of lower motor neuron (LMN) dysfunction include amyotrophy. However, some LMN disorders may rarely cause muscle hypertrophy.

Case Report: A 58-year-old women complained of right inferior limb claudication and calf hypertrophy for four years. She was thoughtfully studied by ortopedics, vascular surgery and rheumatology. Medical history of dislipidemia (suspended statins due to mild CK elevation two years ago). Physical examination showed a right calf circumference of 43cm versus 39cm on the left. Neurologic examination revealed a bilateral decrease in Achilles reflex and hypoesthesia involving the right S1 dermatome, without other abnormalities.

Results: Laboratory screening was normal. Electromyography: nerve conduction studies revealed decreased amplitude of right tibial compound motor action potentials; needle-electromyography disclosed moderate active denervation and chronic neurogenic features of right medial/lateral gastrocnemius and biceps femoris muscles. Lumbar-MRI revealed lumbar canal stenosis with bulging of intervertebral discs and hypertrophy of facet joints and ligamentum flavum justifying radiculopathy secondary to right S1 root compression.

Conclusion: The approach to radiculopathies might be complex, particularly when the clinical manifestations oppose the neurologic cardinal signs. Calf enlargement is an uncommon phenomenon associated with S1 radiculopathy. The pathophysiology remains unclear with literature suggesting the hypertrophy of nondenervated fibers, abnormal stretching of muscle fibers and abnormal electrical activity as three possible mechanisms. S1 radiculopathy should be considered in the differential diagnosis of unilateral calf enlargement, particularly after excluding the most frequent causes.

Disclosure: Nothing to disclose

P3285

Case of delayed radiation thoracic myelopathy with diagnosis of multiple myeloma having history of autologous bone marrow transplant

S. Duman, M. Celebisoy, I. Tatlidil

Izmir Katip Celebi University Ataturk Research and Training Hospital, Neurology, Izmir, Turkey

Background and aims: Delayed Radiation Myelopathy (DRM) is a rare long term progressive and serious complication of radiotherapy. Differential diagnosis of DRM is challenging due to various complications of malignancies. On the other hand there is no curative treatment for DRM which makes defining risk factors and protection of susceptible subjects more important. We describe a case of thoracic delayed radiation myelopathy who has history having multiple myeloma with history of autologous bone marrow transplant (ABMT) and treated with irradiation to thoracic spinal cord due to osteolytic metastasis of spine.

Case Report: A 60-year-old-female patient presented with progressive paraparesis, sensory deficit below T10. Upon admission she was bound to bed. Laboratory test results were unremarkable. Lumbar puncture revealed normal cerebrospinal fluid test results. No sign of infection and primary complication of malignancy were found. Spinal Magnetic Resonance Imaging (MRI) view revealed thickening of distal part of spinal cord with heterogeneous T2 hyperintensity. The patient had history of 2000 rad radiotherapy to inferior thoracic area 14 months before admission.

Results: She was diagnosed as DRM. Pulse steroid therapy was initiated. She was not responsive 10-day-pulse-steoid therapy.

Conclusion: Delayed radiation myelopathy in thoracic segment is rare compared to cervical myelopathy. Most of radiotherapy regimens are tolerable for most of the complications of radiation therapy with low risk of DRM. However, case reports from literature showed that chemotherapy and ABMT reduce the threshold of tolerance for susceptible subjects. Our case is demonstrative to show the relevance of accompanying factors increasing the risk of DRM.

Disclosure: Nothing to disclose

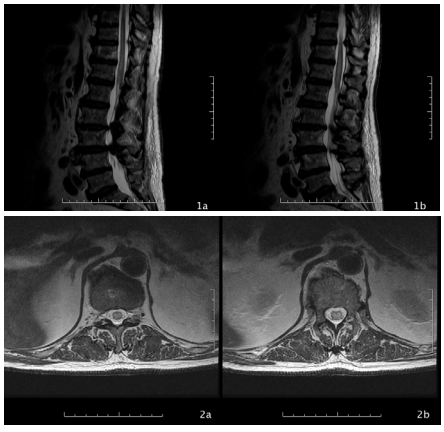
P3286

A rare case of the extensive thoracic and lumbar spinal cord ischemic stroke with fatal outcome

M. Waliszewska-Prosół[1], M. Koszewicz[1], S. Budrewicz[1], M. Ejma[1], P. Szewczyk[2], R. Podemski[1]
[1]Wrocław Medical University, Neurology, Wroclaw, Poland, [2]Wrocław Medical University, General Radiology, Interventional Radiology and Neuroradiology, Wroclaw, Poland

Background and aims: Spinal cord infarctions are diagnostic challenges. They occur infrequently, constitute approximately only 1% of all strokes and may have diverse causes.

Case Report: An 87-year-old man, without past medical history, was admitted to the Neurology Department because of a sudden onset (1 day) lower limbs palsy and loss of sphincter control. The neurological examination revealed: flaccid paraparesis of the lower limbs with areflexia, negative Babinski signs. There were no abdominal reflexes. Pinprick and temperature sensation were absent below the L1 dermatome. Proprioception and vibration sense were intact. Patient was catheterized. MRI of the thoracic and lumbar spine revealed in T2WI images hyperintense area covering the majority of the cross section of the spinal cord from level Th9 to the conus medullaris. In the late follow up MRI this area regressed, only slight spinal cord atrophy was observed. Routine laboratory tests showed elevated D-dimers, but the other tests of blood coagulation were normal as well as CSF. Tumor markers, ANA, anty ds DNA, cANCA, pANCA, antibodies against beta2 glykoprotein and anticardiolipin were within normal limits. He was treated with an osmotic diuretics, steroids and low-molecule weight heparin, with no clinical and radiological improvement. He died 1 month after recognition, because of a pulmonary thrombosis.



Conclusion: We report a fatal case of spinal ischaemic stroke. Clinical observation and atypical extensive changes in MRI, allowed us to make a diagnosis of spontaneous ischemic spinal cord stroke. Because of many diverse causes is should be differentiated from post-traumatic stroke, postoperative damage, myelitis, vasculitis and blood coagulation disorders.

Disclosure: Nothing to disclose

P3287

Secondary resistance to botulinum toxin-A in urinary incontinence caused by spinal cord injury: diagnosis and management

C. Zuliani[1], C. Fattorello Salimbeni[1], F. Cavallari[2], E. Andretta[3]
[1]Department of Neurology, Mirano (Ve), Italy, [2]Department of Surgery, Mirano (Ve), Italy, [3]Department of Urology, Dolo (Ve), Italy

Background and aims: Bladder botulinum toxin-A (BTX-A) injections are routinely used in subjects with neurogenic overactive bladder resistant/intolerant to anticholinergics. This treatment needs to be repeated periodically. Some patients may develop resistance due to neutralizing antibodies formation against the neurotoxin. We evaluated the incidence of secondary non-responder to BTX-A in our Spinal Cord Injury (SCI) casuistry and the usefulness of the Extensor Digitorum Brevis Test (EDB-T) to detect their immunoresistance.

Methods: From 2006 to nowadays, at least 10 out of 63 thoracic SCI patients became completely or partially - mean benefit of 45 days - unresponsive to BTX-A after a mean of 2.5 treatments (range 1-4). 8 out of 10 (6 males and 2 females, mean age 46.5 years) underwent the EDB-T and 7 among them were switched to IncobotulinumtoxinA, a free of complexing protein BTX-A, maintaining the same dose (200 Units). All underwent urodynamic monitoring.

Results: All the patients had detrusor-sphincter dyssinergia. EDB-T confirmed immunoresistance in 7 cases, partial in 3 (although 1 was clinically resistant). The switch to IncobotulinumtoxinA has been effective in the patient resulted responsive to BTX-A at the EDB-T and maintained the same shorter benefit in 2 out of the 3 resulted partial resistant at the EDB-T.

Conclusion: In our experience about 16% of SCI patients become unresponsive to BTX-A. The EDB-T, the initial investigation to confirm secondary immunoresistance, showed its reliability, absolute in 7 cases, relative in 1. Switching therapy to a less immunogenic BTX-A has shown a clinical advantage only in the patient not-resistant at EDB-T.

Disclosure: Nothing to disclose

P3288

Is it true that the combination therapy with aminoglycoside antibiotics enhance the risk of systemic neurotoxic effect of Botulinum toxin A?

C. Zuliani[1], M. Balladelli[2], G. Artuso[3], E. Andretta[3]
[1]Department of Neurology, Mirano (Ve), Italy, [2]Microbiology Unit, Dolo (Ve), Italy, [3]Department of Urology, Dolo (Ve), Italy

Background and aims: Intravesical injections of Botulinum toxin-A (BTX-A) are an effective, safe and well tolerated therapy for neurogenic bladder overactivity refractory/intolerant to antimuscarinics. Their commonest adverse event is Urinary Tract Infection (UTI) thus, especially in recurrent UTIs due to multiresistant bacteria, it is sometime necessary to pre-treat with antibiotics. In these cases Aminoglycosides, even though in some cases they represent the more suitable antibiotic treatment, should be used with caution, as they may interfere with the neuromuscular transmission, and thusenhance the neuromuscular block caused by BTX-A. We report our experience about the assocation iBTX-A and Am used as short therapy.

Methods: From 03/2013 to 02/2014, 23 spinal cord injured (SCI) patients underwent combination therapy with BTX-A (Onabotulinum 200 Units) and Gentamycin (3-5 mg/Kg/ once a day intravenously for 5 days) chosen according to the antibiogram and started on average 2 days before BTX-A injections. Patients had regular follow-up examinations and were also checked by phone daily for 21 days after BTX-A.

Results: No neurological complications were reported. One patient developed UTI with hyperpyrexia, caused by multiresistant Klebsiella Pneumoniae, 2 days after BTX-A and 1 day after suspension of Gentamycin.

Conclusion: The fear that the combination therapy with aminoglycoside antibiotics can enhance the neuromuscular block caused by BTX-A comes from literature of 70s-'80s, where cases of botulism had been reported. Our results do not support these data, probably because BTX-A starts to work when Aminoglycosides has been already eliminated. The combination therapy with BTX-A and Aminoglycosides can therefore be considered feasible and effective to avoid UTI.

Disclosure: Nothing to disclose

Tuesday, June 23 2015
Ageing and dementia 3

P4101
Clinical, functional and behavioural correlates of isolated, subjective memory complaints in rural community-dwelling older adults: data from the Zabùt Aging Project

M. Conticelli[1], A. Aronica[1], A.B. Cefalù[2], R. Monastero[1]
[1]Università di Palermo, Dipartimento Biomedicina Sperimentale e Neuroscienze Cliniche, Palermo, Italy, [2]Università di Palermo, Dipartimento Biomedico di Medicina Interna e Specialistica, Palermo, Italy

Background and aims: Subjective Memory Complaint (SMC) is an issue of growing interest in the study of mild cognitive impairment and dementia. We describe clinical, functional and behavioural correlates of isolated SMC (iSMC) in an Italian community-based sample.

Methods: Subjects were drawn from a 10-year follow-up cohort study of nondemented subjects conducted in an Italian rural village in southern Italy: the Zabùt Aging Project. iSMC was measured using the Memory Assessment Clinic-Questionnaire. Covariates includes: multimorbidity (≥3 disease requiring treatment), number of activities lost in the basic (ADL-l) and instrumental activities of daily living (IADL-l), and the presence of depressive symptoms using the Center for Epidemiological Studies-Depression Scale (CES-D).

Results: 457 subjects (266 controls and 191 iSMC), aged ≥60 years, were included in the study. Cases and controls did not significantly differ regarding demographics and multimorbidity. Contrarily, respondents who reported iSMC showed higher scores in ADL-l ($p<0.001$), IADL-l ($p<0.001$), and CES-D ($p<0.0001$) than those without. After adjustment for demographics, iSMC was independently associated with ADL-l (OR=1.4, 95% CI=1.0-1.8), IADL-l (OR=1.7, 95% CI=1.1-2.7), and with the presence of depressive symptoms (OR=2.4, 95% CI=1.5-3.8). Further adjustment for the apolipoprotein E4 genotype did not modify results.

Conclusion: iSMC independently correlates with functional disability and depression in our population. Prospective analyses from the Zabùt cohort as well as data from other longitudinal, population-based, cohorts would be useful in examining the prognostic role of iSMC in nondemented subjects.

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P4102
Posterior cortical atrophy: a clinical case series and literature review

A. Nelson[1], S. Pal[2]
[1]University of Edinburgh, University of Edinburgh Medical School, College of Medicine and Veterinary Medicine, Edinburgh, United Kingdom, [2]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom

Background and aims: Posterior Cortical Atrophy (PCA) is a striking neurodegenerative syndrome characterised by visuoperceptual impairment with eventual decline in wider cognition and occipitoparietal abnormalities identified on neuroimaging. Debilitating visual symptoms including loss of facial recognition, impaired depth perception, difficulty reading and loss of writing ability occur, with heterogeneous underlying pathology including Alzheimer's Disease (AD) identified at post-mortem. Despite being characterised 25 years ago, no validated diagnostic criteria incorporating clinical phenotypic and biomarker findings exist. We present a case series of patients with review of the literature.

Methods: Patients with PCA were identified clinico-radiologically and details of their clinical progression, including history, cognitive examination, neuroimaging, including MRI (T1 volume, T2 and FLAIR) and 99mTc-HMPAO SPECT scans, and CSF, extracted from patient records.

Results: Patients were referred from various services. Visuospatial deficits were common including inability to see movement, impaired object recognition, night blindness, face blindness, visual hallucinations and impaired depth perception. Other common deficits included loss of reading, writing and calculation ability, reduced fluency, impaired working memory and eye movement incoordination. Neuroimaging identified occipitoparietal abnormalities. CSF examination revealed changes in beta amyloid and phosphorylated tau suggestive of AD in 50%. Cholinesterase inhibitors yielded subjective symptomatic benefit in 71%.

Conclusion: PCA diagnosis is based on occipitoparietal symptoms, supported by imaging findings. In our series, HMPAO-SPECT was more sensitive than MRI in diagnosing PCA and more commonly detected laterality and frontal lobe involvement. Anti-cholinesterase treatment resulted in subjective benefit suggesting the need for future prospective randomised controlled trials of symptomatic treatments.

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P4103
Abstract cancelled

P4104

Mechanisms of glutamate recycling and replenishment at mammalian synapses

N. Senaratne[1], B. Billups[2]
[1]University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom, [2]University of Cambridge, Department of Pharmacology, Cambridge, United Kingdom

Background and aims: The glutamate-glutamine cycle is disrupted in a variety of neurodegenerative conditions such as Alzheimer's disease and Huntington's chorea. Electrophysiological evidence that this cycle is important during synaptic transmission has been inconsistent. We assessed the physiological importance of astrocytic recycling at the cerebellar mossy fibre-granule cell synapse by inhibiting the glutamate-glutamine cycle pharmacologically and assessing its effect on neurotransmitter pools.

Methods: Cerebellar slices were taken from Wistar rats 16-21 days old. We extracellularly stimulated mossy fibres at 50Hz using thick-walled glass pipettes. mEPSCs from whole-cell voltage-clamped granule cells were identified using a threshold of 7mV. We inhibited presynaptic glutamine uptake with 20mM of either the system A antagonist α-(methylamino)isobutyric acid (MeAIB) or the multi-system inhibitor histidine.

Results: 6 cells were patched from 6 animals. mEPSC amplitudes were stable over time, varying by 1.0±1.13 pA over 10 mins (7±8% change; n=7 cells; p=0.40). Neither MeAIB or histidine significantly reduced mean mEPSC amplitudes (Fig 1A): 9.9±9.6% reduction for MeAIB (p=0.38, n=4 cells); 12±9% reduction for histidine (n=2 cells).

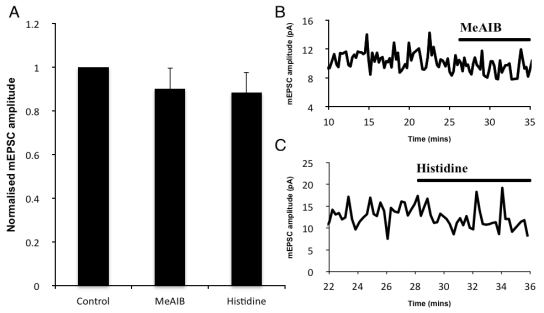

Figure 1: A: Mean granule cell EPSC amplitudes. B + C: Example time courses for single patched cells.

Conclusion: A functional glutamate-glutamine cycle is not necessary for neurotransmission at the cerebellar mossy fibre-granule cell synapse. This contrasts with studies of cortical, hippocampal and brainstem synapses and highlights how neurotransmitter recycling mechanisms vary across the mammalian brain. These results hint that disruption of the cycle may only contribute to neuropathology at specific neuronal locations, a novel concept for neurodegenerative conditions such as Alzheimer's disease and Huntington's chorea.

Disclosure: Nothing to disclose

P4105

Zarit Burden Interview: a possible informant-based diagnostic test for dementia?

B. Stagg[1], A.J. Larner[2]
[1]Alzheimer's Society, Liverpool, United Kingdom, [2]Walton Centre for Neurology and Neurosurgery, Cognitive Function Clinic, Liverpool, United Kingdom

Background and aims: To report the diagnostic accuracy of the Zarit Burden Interview (ZBI) used as an informant screening questionnaire for the detection of dementia and cognitive impairment, and its comparison with patient performance measures, Mini-Mental State Examination (MMSE) and mini-Addenbrooke's Cognitive Examination (m-ACE).

Methods: Prospective observational study, Cognitive Function Clinic.

Results: In 37 consecutive patient-spouse dyads seen over a 5-month period (July-December 2014; patient F:M = 10:27; age range 30-85 years, median 67 years), 14 patients were diagnosed with dementia, 14 with MCI, and 9 with subjective memory impairment (SMI) only. Full, short, and screening ZBI versions (22, 12, and 4-items respectively) showed overlapping scores for each diagnosis, and no correlation with patient age, MMSE, or m-ACE scores. Mean ZBI scores did not differ significantly between dementia and no dementia (= MCI + SMI) groups, or between cognitive impairment (= dementia + MCI) and no cognitive impairment (SMI) groups. Mean MMSE and m-ACE scores differed significantly between cognitive impairment and no cognitive impairment groups.

Conclusion: ZBI is simple to administer and acceptable to informants, but did not prove effective as an informant-based measure for dementia diagnosis. Caregiver burden appears to be largely independent of degree of cognitive impairment, and hence requires dedicated assessment to plan appropriate interventions.

Disclosure: Nothing to disclose

P4106

What is the current practice of cognitive and motor screening in dementia clinics? A world-wide on-line survey.

A. Symonds, T. Bak
University of Edinburgh, Edinburgh, United Kingdom

Background and aims: Motor dysfunction is increasingly recognised as an important feature of dementias and other cognitive disorders. However, in contrast to cognitive assessment the practice of motor examination is less consistent.

Methods or Materials or Case Report: In order to determine the current practice regarding cognitive and motor examination in dementia clinics, we distributed a brief 10 question on-line survey in 10 different languages to dementia clinics across the world.

Results: We have received 317 responses from 31 countries, mostly from neurologists, psychiatrists and geriatricians. Most clinicians estimated the frequency of motor symptoms in dementia clinic patients as 0-20%, lower than that reported in the literature. Non-disease specific cognitive screening tools (most commonly the Mini Mental State Examination (MMSE) were used by 98% of clinicians. Depending on specialty, only 35–75% of clinicians routinely performed a motor exam and only 30% used a motor screening test. All motor screening tests were disease-specific; the most widely used was Unified Parkinson's Disease Ratings Scale (UPDRS) -III.

Conclusion: Cognitive screening, most often using validated tools such as MMSE, forms an integral part of dementia assessment across the world. In contrast, the practice of motor examination varies depending on specialty and the frequency of motor symptoms tends to be underestimated. While the cognitive screening tests can be applied to many forms of dementia, the motor screening tools are disease-specific (e.g. UPDRS-III). We argue that the development of a generally applicable motor screening tool could increase the frequency of motor examination and enhance the awareness of motor symptoms in dementia.

Disclosure: Nothing to disclose

P4107

Evidence of diffusion-weighted MRI abnormalities one year prior to the onset of sporadic Creutzfeldt-Jakob disease

F. Verde[1], N. Ticozzi[1], S. Messina[1], N. Calcagno[1], E. Scola[2], F. Girotti[1], A. Falini[3], F. Tagliavini[4], V. Silani[1]
[1]Istituto Auxologico Italiano, Neurology, Milan, Italy, [2]Fondazione IRCCS Ospedale Maggiore Ca' Granda, Neuroradiology, Milan, Italy, [3]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy, [4]IRCCS Istituto Neurologico C. Besta, Neuropathology, Milan, Italy

Background and aims: We describe a case of sporadic Creutzfeldt-Jakob disease (sCJD) with restricted diffusion on magnetic resonance imaging (MRI) one year prior to clinical onset.

Case Report: A 65-year-old woman with headache underwent brain MRI showing diffusion-weighted imaging (DWI) hyperintensity in the right basal temporo-occipital cortex (figure 1). A diagnosis of ischaemic lesions was made. After 12 uneventful months, she began to develop rapidly progressive mental deterioration. Almost concomitantly, she was diagnosed with breast cancer, which was surgically removed. Two months later, she was admitted to our neurology unit.

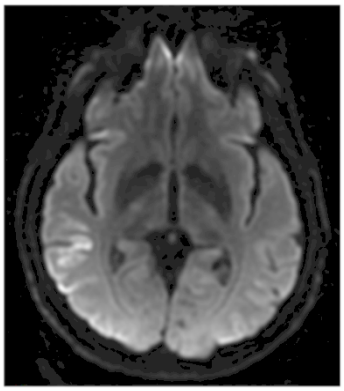

Fig. 1 Diffusion-weighted image from the MRI performed in June, 2013, showing hyperintensity of the right basal temporo-occipital cortex (3 Tesla scan)

Results: Neurological examination was notable for reduced initiative, impairment of memory and abstract thinking, ideomotor apraxia, and visual agnosia. Neuropsychological evaluation demonstrated severe multidomain deterioration. Brain MRI showed extension and contralateral spread of the previous abnormalities (figure 2). Electroencephalogram (EEG) displayed delta-wave slowing on the right hemisphere. Cerebrospinal fluid (CSF) analysis demonstrated normal protein, glucose, and cells, and absence of autoantibodies, but raised tau protein and detectable 14-3-3 protein. A diagnosis of sCJD was made.

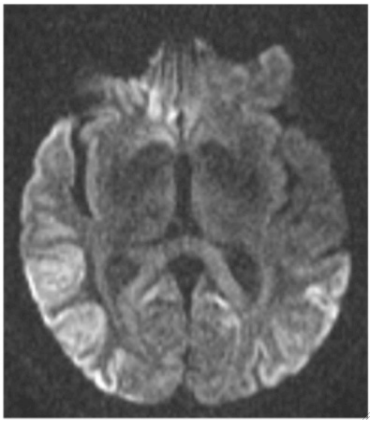

Fig. 2 Diffusion-weighted image from the MRI performed in September, 2014, demonstrating extension of the previously documented signal abnormalities, with bilateral involvement of basal temporo-occipital and parietal cortices, more marked on the right (1.5 Tesla)

Conclusion: Our case demonstrates that cortical restricted diffusion can be detectable on MRI up to one year before clinical onset of CJD, implying that prion protein deposition is an early event. Our findings could also suggest a possible role of DWI in predicting disease onset in familial cases. From a clinical standpoint, this case highlights that CJD should be considered not only in the contex of rapidly progressive dementia, but also when compatible MRI abnormalities are found incidentally in a cognitively normal person.

Disclosure: Nothing to disclose

P4108

Characteristics of depressive symptoms in patients with early-onset Alzheimer's disease by disease severity

B. Yoon[1], K.O. Lee[1], Y.S. Shim[2], H.J. Kwag[3]

[1]Konyang University Hospital, Department of Neurology, Daejeon, Korea, Republic of, [2]Bucheon St. Mary's Hospital, Department of Neurology, Bucheon, Korea, Republic of, [3]Daejeon Veterans Hospital, Department of Neurology, Daejeon, Korea, Republic of

Background and aims: Depression shows higher incidence in early-onset Alzheimer's disease (EOAD). However, it is uncertain whether they change by disease severity and which depressive symptoms are more frequent in each disease stage. We investigated the differences in incidence and characteristics of depressive symptoms by dementia severity in EOAD patients.

Methods: We enrolled 412 EOAD patients. The 15-item Korean version Geriatric Depression Scale (GDS-15) was administered to participants. We subdivided into 3 groups by disease severity: very mild (CDR 0.5, 191) vs mild (CDR 1, 180) vs moderate (CDR 2, 41). We compared individual GDS-15 items among 3 groups.

Results: The incidence of depression by cut-off value appeared relatively lower in moderate group (23.1%) than other groups (very mild 37.2%, mild 44.4%) (P=0.026). Three factors were generated, which were hopelessness/negative thoughts(items 6,8,12,14,15), unhappiness/unsatisfaction (items 1,3,5,7,11), and monotony/lack of energy (items 2,4,9,10,13). Except for memory complaints (10), monotony/lack of energy (2,13) were reported most frequently regardless of severity. Very mild and mild groups complained more memory problems than moderate group(P=0.001). Moderate group complained statistically less about unhappiness/unsatisfaction (1, P=0.048; 5, P=0.049; 11, P=0.036). Mild group showed tendency for more hopelessness/negative thoughts (12, P=0.054; 14, P=0.067).

Conclusion: Symptoms by monotony/lack of energy were highest in all groups, however, depressive symptoms by unhappiness/unsatisfaction significantly decreased at moderate stage. Moreover, mild group demonstrated tendency to feel hopelessness/negative thoughts higher. In conclusion, disease severity itself influenced incidence of depression and different characteristics according to disease severity in EOAD.

Disclosure: Nothing to disclose

Clinical neurophysiology 3

P4109

Contralateral aberrant reinnervation in patients with pudendal nerve injury

J. Baron Sanchez[1], G. Lacima[2], R. Arca[3], M. Morales[3], C. Cabib[3], J. Valls-Solé[3]

[1]Hospital Clinico de Valladolid, Neurology, Valladolid, Spain, [2]Hospital Clinic Barcelona, Gastroenterology, Barcelona, Spain, [3]Hospital Clinic Barcelona, Neurology, Barcelona, Spain

Background and aims: Reinnervation after peripheral nerve injuries implies abnormal branching of regenerating axons, modification of the original distribution of muscle innervation and compensatory activity in neighbouring nerves. These may lead to an abnormal function in muscles that require fine motor control, such as sphincters. We investigated if external anal sphincter (EAS) dysfunction leading to incontinence was related to pudendal nerve reinnervation abnormalities.

Methods: In 10 patients with fecal incontinence and 3 controls, we applied focal electrical stimuli with a monopolar needle inserted into one side and recorded responses in the other side. We hypothesized that the size of the contralateral responses would be an indirect measure of the amount of abnormal contralateral reinnervation. We also recorded EAS needle EMG activity and pudendal nerve latency.

Results: 8 patients had abnormal needle EMG findings (denervation or significant jitter/blocking). Mean pudendal nerve latency was 2.9 ms, with absent responses in 2 cases. Patients had significantly larger contralateral responses that occurred at a shorter latency than in controls (response area of 625 μVxms in patients vs 14 μVxms in controls, and response latency of 11.7 ms in patients and 19.5 ms in controls).

Conclusion: Abnormal reinnervation of sphincter muscles after pudendal nerve lesion is a likely cause of anal sphincter dysfunction in patients with faecal incontinence.

Disclosure: Nothing to disclose

P4110

Abstract cancelled

P4111

Computer-assisted thermal threshold testing - our experience and normative data

V. Potockova[1], R. Mazanec[1], J. Schlenker[2]

[1]Charles University in Prague, [2]nd Faculty of Medicine, Motol University Hospital , Department of Neurology, Prague, Czech Republic, [2]Czech Technical University in Prague, Faculty of Biomedical Engineering, Prague, Czech Republic

Background and aims: Computer-assisted thermal threshold testing (TTT) is a quantitative psychophysical method that allows to test small nerve fibers (type Aδ and C). It is an integral part of diagnostics of small fiber neuropathy (SFN) which is undetectable using standard electrophysiological techniques (conduction studies, needle electromyography). The most common cause of SFN is diabetes mellitus (DM), already in preclinical stage, i.e. impaired glucose tolerance. The aim was to create our own normative data and compare it with previously published papers.

Methodst: We tested 50 healthy subjects (25 F + 25 M, 5 persons in each decade from 20 to 70 years). We determined cold and warm detection threshold (CDT, WDT) on both extremities and body sides (thenar, tibia, dorsum). We examined by means of a Peltier-based thermal stimulator (SENSELab - TERMOTEST MSA, contact probe 25x50mm, Somedic, Sweden). As an investigative algorithm we used a non-randomized method of limits (reaction time inclusive technique). Exclusion criteria included the absence of the most frequent causes of SFN (DM, hyperlipidemia, chronic alcohol abusus) and other symptoms of peripheral or central nervous system impairment (cerebrovascular, autoimmune, infectious, metabolic or toxic).

Results: CDT, WDT (Table 1). We found a statistically significant decrease of CDT and increase of WDT values in lower against upper extremities. We did not prove statistically significant influence of gender and age on the values of thresholds.

CDT (°C)	Thenar	Tibia	Dorsum
Median	30,3	29,8	29,6
Average	30,1	29,5	28,9
5th percentile	28,9	27,1	25,1
WDT (°C)	**Thenar**	**Tibia**	**Dorsum**
Median	34,0	39,1	38,3
Average	34,2	39,4	38,7
95th percentile	35,5	44,3	43,7

Table 1. Values of CDT (cold detection threshold) and WDT (warm detection threshold)

Conclusion: Thermal threshold testing is an important tool of diagnostics of SFN. This method is relatively time-saving and non-invasive, but requires a training of medical staff and appropriate laboratory conditions.

Disclosure: Nothing to disclose

P4112

Neurophysiological follow-up of patients with celiac disease on gluten-free diet: a TMS study

V. Puglist[1], L. Vinciguerra[1], R. Ricceri[1], M. Cantone[1], G. Lanza[2], M. Pennisi[3], C.C.D'Agate[1], R. Ferri[2], S. Giuffrida[1], R. Bella[1]

[1]University of Catania, Catania, Italy, [2]Sleep Research Centre, Department of Neurology, I.C., Oasi Institute (IRCCS), Troina, Italy, [3]Emergency Hospital "Cannizzaro", Catania, Italy

Background and aims: A recent investigation showed that Transcranial Magnetic Stimulation (TMS) might disclose a subclinical neurological involvement in patients with celiac disease (CD). Here we aim to compare TMS measures before and after the gluten-free diet in order to monitor the observed changes and to assess the impact on the diet cortical excitability.

Methods: A sample of 13 patients from the original cohort of 20 was re-evaluated after approximately 2 years of an adequate course of gluten-free diet. Antibodies were still present in 3 and were borderline in 2. A screening for cognitive and neuropsychiatric symptoms was repeated as well as the evaluation of cortical excitability by means of single and paired-pulse TMS from the first dorsal interosseous muscle of the dominant hand.

Results: Compared to baseline, patients showed a significant decrease of the median resting motor threshold (34 vs 35%, $p<0.01$) and a shorter central motor conduction time (3.8 vs 4.8 ms, $p<0.01$). Depressive symptoms, quantified with the Hamilton Depression Rating Scale, improved (2.8 vs 5.6, $p<0.01$).

Conclusion: A global increase of cortical excitability together with a faster conductivity along the cortico-spinal tract was observed in gluten-free diet patients, without significant changes of the other TMS measures found at baseline. These findings may represent a neurophysiological evidence that immune system dysregulation might persist despite the alimentary therapy, although the diet seems to enhance the excitability and conductivity of the central motor pathways. The impact of the gluten-free diet on subclinical neurological abnormalities needs to be further explored.

Disclosure: Nothing to disclose

P4113

Epidermal recordings can be used for preclinical functional assessment of visual pathways.

R. Santangelo[1], V. Castoldi[1], M. Cursi[1], L. Chaabane[1], G. Comi[2], L. Leocani[3]

[1]Scientific Institute and University San Raffaele Hospital, Department of Neurology and INSPE-Institute of Experimental Neurology, Milan, Italy, [2]University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy, [3]Scientific Institute San Raffaele, Department of Neurology, Milan, Italy

Background and aims: Visual Evoked Potentials (VEPs) are a powerful tool to evaluate the electrical conduction along the visual pathways, both in humans and in preclinical models.Traditionally, epidural screw electrodes are used to record VEPs in preclinical research. Here we tested the feasibility, in rat models, of the same technique used for VEPs in humans, i.e. epidermal cup electrode recording, avoiding invasive surgical procedures

Methods: 7 Dark Agouti (DA) rats underwent VEP recording through epidermal 6mm Ø Ag/Cl cup electrodes (cup recorded, CR). Flash VEPs from both eyes were recorded under sevoflurane volatile anesthesia once a week for 6 weeks, measuring P1 latency from N1-P1-N2 complex. P1 latencies from CR rats were compared to P1 latencies from 7 age-matched DA rats which underwent epidural VEP recordings through stainless screw electrodes (screw recorded, SR) at the same time points. P1 latency mean values were compared using the ANOVA for repeated measures or the Conover's free distribution method, a non-parametric ANOVA based on ranks in case of data not normally distributed.

Results: Morphologically, VEP traces obtained with screw and cup electrodes were comparable and P1 wave was clearly detectable. Neither significant effects nor interactions of the main factors "time" and "type of electrode" were found on VEP latencies.

Conclusion: Epidermal electrodes can provide VEP waves comparable with traditional more invasive epidural recordings. Further studis are needed to compare their value in assessing and monitoring preclinical models of neurological diseases

Disclosure: Part of this work was financially supported by Merck Serono S.A., Geneva, Switzerland. Merck Serono is the biopharmaceutical division of Merck KGaA, Darmstadt, Germany.

P4114

Frequency of accessory deep peroneal nerve: electrophysiological study

O. Sinanovic, S. Zukic, N. Piric
University Clinical Center Tuzla, Neurology, Tuzla, Bosnia and Herzegovina

Background and aims: The different anatomical anomalies of peripheral nerves occur with various frequencies in the population. ADPN nerve has been regarded as an anomalous, derived from the superficial peroneal nerve or its branch and supplies motor innervations for extensor digitorum brevis (EDB). The EDB is usually innervated exclusively by the deep peroneal nerve, however, one or both of the EDB muscles are (partially or exclusively) innervated by the ADPN. Electromyography lab is the best environment for detecting presence and prevalence of this nerve, so present study enrolled.

Methods: In this ongoing cross sectional descriptive study 138 cases comprising 276 legs referred for electrodiagnostic studies to Electromyography Lab, Department of Neurology, University Clinical Center Tuzla participated in the study. Compound muscle action potential (CMAP) and Nerve conduction Velocity (NCV) of Deep Peroneal Nerve (DPN) were measured using EMG machine by stimulating DPN at knee, ankle and lateral malleolus areas accordingly, with recording from extensor digitorum brevis muscle.

Results: The study included 75 females (54.3%) and 63 (45.7%) males with mean age of 46.8±17.0. ADPN was detected in 27 (19.50%) patients. Among them, 6 (22.2%) had bilateral ADPN and in remaining 21 (77.8%) ADPN was unilateral (6/22.2% on right, and 15/55.5% on left side).

Conclusion: The frequency of ADPN in this electrophysiological study was 19.50% (22.2% bilateral and 77.8% unilateral). This common anatomical variation has to be known in order to avoid errors in interpreting the peroneal NCV with detection on the EDB.

Disclosure: Nothing to disclose

P4115

A neurophysiological investigation of a large population of patients affected with Kennedy's disease (SBMA) confirms diffuse neurological involvement

M. Volpe[1], G. Zara[2], G. Querin[1], C. Bertolin[1], F. Zoccarato[1], E. da Re[1], E. Volpato[1], D. Pareyson[3], M. Ermani[1], G. Sorarù[1]
[1]Università di Padova, Neuroscienze, Padua, Italy, [2]Azienda Ospedaliera di Padova, Neuroscienze, Padua, Italy, [3]Istituto Neurologico C. Besta, Milan, Italy

Background and aims: Spinal and Bulbar Muscular Atrophy (SBMA) is a rare motor neuron disease due to a CAG repeat expansion in the androgen receptor gene. Growing evidence suggest a diffuse neurological involvement, other than motorneuron, such as muscular primitive damage and autonomic impairment, moreover respiratory involvement is considered negligible by some authors. There are no data in literature about phrenic nerve conduction study (NCS) and Sympathetic Skin Response (SSR), very few about Blink Reflex (BR) and there is a lack of detailed descriptions of needle electromyography (EMG) features in different muscular districts.

Methods and Materials: 69 genetically confirmed SBMA patients underwent phrenic NCS, SSR, BR and EMG of cranial district, upper and lower limb.

Results: Distal latency of the phrenic nerve compound muscle action potential (cMAP) was abnormally prolonged in 61.2% of the right side and 52.2% of the left side studies. Nor distal latency or amplitude of cMAP correlated with forced vital capacity or CAG repeat size. Average latency of the SSR is significantly longer in our patients group when compared with normal subjects. BR showed a prolonged latency of R1 response in 9 cases, who also showed altered sensory NCS of median, ulnar and sural nerves. EMG confirmed a chronic neurogenic pattern, but medial gastrocnemius showed low amplitude motor unit action potentials in 44.9% patients and a pattern suggestive for fibroadipose substitution.

Conclusion: Our pure neurophysiologic data from an unusually numerous population of patients seem to confirm subclinical diffuse neurological involvement and question the real entity of the respiratory disturbance in SBMA.

Disclosure: Nothing to disclose

Epilepsy 4

P4116

Non-convulsive status epilepticus in the elderly

H.M. Delgado[1], V. Silva[2], R. Pinto[2], N.M.M. Canas[2]
[1]CHLO, Neurology, Lisbon, Portugal, [2]HBA, Neurology, Loures, Portugal

Background and aims: The incidence of epilepsy is highest in the elderly, frequently presenting with non-convulsive status epilepticus (NCSE); the early recognition of the clinical manifestations and etiologies of NCSE can directly influence its associated morbidity/mortality. We describe the clinical features, etiology and outcome at discharge of a cohort of elderly patients with NCSE.

Methods: Retrospective study of patients ≥65 years old and EEG criteria for EMNC diagnosed in our hospital (2012-2014).

Results: We identified 31 patients (17 women), mean age 79 years-old (65-90), 71% without history of epilepsy; 55% had a diagnosis of dementia or motors deficits prior to admission. Although 33% patients had "de novo" focal neurologic signs, 90% presented with behavior/consciousness changes. NCSE was provoked in 74.2% of patients (mostly metabolic/infectious causes), a third of them with remote structural damage in neuroimaging studies (stroke, post-trauma). In only 22.6% the clinical diagnosis of NCSE was considered before EEG confirmation, mostly in the sequence of an isolated seizure with motor features; in the great majority of the others, the clinical features were attributed to the underlying dementia/ encephalopathy due to medical causes. In 35.5% of patients, NCSE was controlled with one antiepileptic, with levetiracetam the most widely used. 22.6% died and 16.1% had new or worsening of previous deficits.

Conclusion: In the elderly, the high prevalence of dementia and medical comorbidities may obscure the recognition of NCSE. This diagnosis should be suspected in patients with behavior/awareness changes, especially if they present a seizure with motor component or lesions with cortical involvement.

Disclosure: Nothing to disclose

P4117

A multicenter survey of clinical experience with perampanel in Spain - study of 187 patients.

V. Garayoa Irigoyen[1], J.A. Mauri Llerda[2], M.J. García Gomara[3], I. Garamendi Ruiz[4], A. Marinas Alejo[5], I. Garcia Morales[6], M. Adúnez Sarasola[4], E. García García[7], C. Arcos Sánchez[8], E. Muñoz Farjas[9], S. Santos Lasaosa[10], J.A. Olivan Usieto[11], L. Diaz de Cerio Julian[12], V. Bertol Alegre[10]
[1]Hospital Universtario Miguel Servet, Department of Neurology, Saragossa, Spain, [2]Saragoza, Spain, [3]Hospital Royo Villanova, Department of Neurology, Saragossa, Spain, [4]Hospital de Cruces, Department of Neurology, Baracaldo, Spain, [5]Hospita de Cruces, Department of Neurology, Baracaldo, Spain, [6]Madrid, Spain, [7]Department of Neurology, Madrid, Spain, [8]Hospital General de la Defensa, Saragossa, Spain, [9]Hospital de Alcañiz, Alcañiz, Spain, [10]Saragossa, Spain, [11]Alcañiz, Spain, [12]Mahon, Menorca, Spain

Background and aims: Perampanel (PER) has been recently approved for adjunctive treatment of partial-onset seizures from age 12 years on. This study was focused on evaluating the response to treatment with PER as adjunctive therapy in patients with drug-resistant focal epilepsy.

Methods: We recorded and retrospectively analysed 187 patients treated with PER from eight different Spanish centres. Patients should be monitored at least 6 months. Background characteristics of different variables were compared with the improvement in seizure frequency, using chi-square test for heterogeneity, or T-student or variance analysis for quantitative variables.

Results: There were 59% women and 41% male with a median age of 40 years (P25-75:33-49) and median duration of epilepsy of 26 years (P25-75:13-36). Etiology was symptomatic in 58% of the cases. Median prior antiepileptic drugs (AED) was 8 (P25-75:4-9) and median number of AED at time of PER association was 2 (inductor 41%, partially inductor 23%). Median time on treatment with PER was 9.2 months (P25-75:6.6-10.2). Responder rate was 45% (6.5% seizure-free). 33% of patients experienced side effects; most frequent were dizziness (9%), somnolence (9%) and irritability (8%). Retention rate was 71% (discontinuation: 12% inefficiency, 8% adverse effects and both 9%). The patients group with secondary generalization showed a 16% (IC:2-30) more improvement than those without generalization (p 0.03). No other variables studied showed significant correlation with the degree of improvement.

Conclusion: The adjunctive treatment with PER may lead to at least temporary freedom of seizures in difficult-to-treat partial epilepsy. However, adverse events are not unusual.

Disclosure: Nothing to disclose

P4118

Abstract cancelled

P4119

Research of CYP2C9 and CYP2C19 gene polymorphism in evaluation of treatment effectiveness in children with epilepsy

V.I. Guzeva[1], V. Guzeva[2], O. Guzeva[2]
[1]Saint Petersburg, Russian Federation, [2]Saint-Petersburg State Pediatric Medical University, Neurological Department, Saint-Petersburg, Russian Federation

Background and aims: It is proved that the genetic polymorphism is the basis of individual sensitivity to drugs and established the important role of gene polymorphisms of cytochromes P450 system in metabolism of anticonvulsants.

Methods: We studied genes CYP2C9 and CYP2C19 system P450 in 86 children with severe forms of epilepsy: 46 (53.49%) were boys and 40 (46.51%)- girls, age was 3 months till 17 years.

Results: As a result of comprehensive survey found that 26 (30.23%) of children had generalized symptomatic epilepsy, 9 (10.47%) children- epileptic encephalopathy (West syndrome and Lennox-Gastaut syndrome), 47 (54.65%) children – symptomatic focal epilepsy (with secondary generalization and without it) and 4 (4.65%) children – idiopathic forms of epilepsy (generalized and focal). We identified 36 children with treatment-resistant epilepsy, children with non-resistant forms of epilepsy, accompanied by complications from taking antiepileptic drugs and 43 (50%) children with polymorphic genes CYP2C9 and CYP2C19. The study showed that the average daily dose of valproate in all children with polymorphic genes to genetic testing exceeded the average daily dose of valproate in children who do not have polymorphic genes.

Conclusion: In 50% of children with severe epilepsy identified gene polymorphism CYP2C9 and CYP2C19 system P450 and in 41.86% cases of rare genotypes established in children with resistant forms of disease. Therefore, treatment of these children should be based on result of genetic research, which determines the presence or absence of polymorphic genes of system P450.

Disclosure: Nothing to disclose

P4120

Abstract cancelled

P4121

Seizure recurrence after AED discontinuation in children

M. Impellizzeri, M. Maione, G. Fanelli, E. Leopizzi, G. Comi, F. Minicucci
Scientific Institute Vita-Salute University San Raffaele, Neurology, Milan, Italy

Background and aims: The discontinuation of antiepileptic drugs (AED) is a challenging issue in epileptic children. The percentage of children who are undergoing AED withdrawal is higher than that of adult patients, and the period of seizure remission before considering treatment withdrawal is shorter. Although the literature on AED withdrawal is focused on the pediatric population, few guidelines are actually provided. The aim of this study is to assess factors that can predict seizure recurrence after AED discontinuation in pediatric patients.

Methods: 42 children, with age of onset of seizures <14 years, were evaluated. Variables analyzed were: family history of epilepsy, type of epilepsy, duration of disease, type and number of AED at time of discontinuation, neuroimaging and electroencephalographic features. These patients achieved complete seizure control for a minimum period of 2 years, and therefore discontinued antiepileptic therapy. The follow-up lasted 2 years.

Results: 35.7% of children relapsed within 2 years. The highest frequencies of recurrence were observed in patients with epilepsy of unknown cause (recurrence rate 63.6%) compared to other forms of epilepsy (recurrence rate 20.7%; OR 0.199). Moreover, the recurrence rate was doubled in children with focal seizures with secondary generalization (recurrence rate 60%) if compared to those with focal seizures without secondary generalization (recurrence rate 29.4%).

Conclusion: These results provide more information to the literature about seizure recurrence in pediatric patients after AED discontinuation. Due to the small sample, a larger cohort of patients should be analyzed in order to increase validity and better understand these variables.

Disclosure: Nothing to disclose

P4122

Non-hyperammonemic reversible valproate-induced encephalopathy after long term treatment

J. Devianne[1], I. Raynouard[1], D. Buch[1], B. Crepon[2], F. Pico[1]
[1]hopital de versailles, neurology, [2]RadiNeurology Department, Versailles Mignot Hospital, Versailles, France

Background and aims: Encephalopathy is an unusual but severe adverse effect of valproate, a widely-prescribed drug in neurology and psychiatrics. Its mechanisms have not been fully understood yet, although its frequent association with hyperammonemia makes it the most often quoted cause.

Case Report: We report a patient with Valproate-induced encephalopathy (VIE) and normal ammoniemia level after long term treatment.

Results: This 62-year-old patient, with type 2 diabetes and hypertension, had a 25 years treatment by valproate (1g twice a day) and phenobarbital (100mg twice a day), in the setting of post traumatic epilepsy. He presented with acute confusion and cognitive decline. The electroencephalogram showed slow rhythms with an anterior maximum that were compatible with a nonconvulsive status epilepticus. A treatment by clonazepam and phenytoin was not associated with any improvement. The following exams were normal: liver and kidney function, blood tests, plasmatic ammonemia, valproate and phenobarbital plasma levels. Follow up encephalogram showed an increase of slow rhythms and triphasic waves appearance, associated with gradual deterioration over a week. Valproate treatment was stopped, and there was a dramatic improvement of the patient's neurologic status. He could be discharged home, with levetiracetam in place of valproate.

Conclusion: The possible occurrence of VIE even after a long-term treatment should be well known by physicians, and should not be dismissed if ammonemia normal. This case could suggests that hyperammonemia is not the only mechanism of VIE.

Disclosure: Nothing to disclose

P4123

Benefits of European cooperation in clinical neuroscience: outcome of epilepsy surgery in a cohort of Slovenian patients treated in collaboration between Ljubljana and Erlangen, Germany

A. Cus[1], D. Gosar[2], H. Hamer[3], B. Kasper[3], K. Rössler[4], H. Stefan[3], M. Buchfelder[4], D.B. Vodušek[1], E. Pauli[3], B. Lorber[1]
[1]University Medical Centre, Ljubljana, Department of Neurology, Ljubljana, Slovenia, [2]University Medical Centre, Ljubljana, Department of Pediatric Neurology, Ljubljana, Slovenia, [3]Neurologie, Epileptologie, Erlangen, Germany, [4]University Hospital Erlangen, Department of Neurosurgery, Erlangen, Germany

Background and aims: For patients with medically intractable epilepsy, neurosurgery is suggested as a treatment option, providing long-term seizure freedom in two thirds of temporal lobe resections and lower success rates in extratemporal resections (Téllez-Zenteno et al. 2005). In small countries functional neurosurgery programs are faced with limited potential for intraoperative diagnostic procedures and neurosurgical expertise because of lack of adequate "high volume" of patients necessary for clinical excellence. To overcome such limitation, the Department of Neurology at University Medical Centre in Ljubljana, Slovenia has established collaboration with the Epilepsy Centre at University Hospital in Erlangen, Germany. In order to evaluate the surgical treatment of Slovenian epilepsy patients abroad, we performed a long-term follow-up study.

Methods: Data were obtained from medical records and an additional follow-up assessment was performed. We evaluated seizure and medication outcome, psychiatric comorbidity, neuropsychological and psychosocial outcome and patient satisfaction.

Results: Between 2001 and 2012 a total of 53 Slovenian adult patients underwent surgical treatment in Erlangen. Nearly 90% suffered from temporal lobe epilepsy. 61% of patients were completely seizure-free and an additional 28% were free of disabling seizures. Cognitive decline after surgery was rare and de novo mood disturbances were mostly of a transient nature. Surgical treatment did not impact employment status. The majority of patients (89%) felt that the surgical treatment largely fulfilled their expectations.

Conclusion: This study demonstrates that cross-border collaboration in epilepsy surgery can be a very effective way to treat epilepsy patients even if important differences in native languages exist between the treating institutions.

Disclosure: Nothing to disclose

Motor neurone diseases 3

P4124

Structural neural correlates of cognitive and behavioural impairment in motor neuron disease

F. Agosta[1], P.M. Ferraro[1], E.G. Spinelli[1], E. Canu[1], N. Riva[2], M. Copetti[3], E. Prudente[4], A. Chiò[5], S. Iannaccone[6], A. Falini[7], G. Comi[2], M. Filippi[1]

[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Neuroimaging Research Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neurology, Milan, Italy, [3]IRCCS-Ospedale Casa Sollievo della Sofferenza, Biostatistics Unit, San Giovanni Rotondo, Italy, [4]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Neuroradiology, Milan, Italy, [5]University of Turin, Department of Neuroscience, Turin, Italy, [6]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Clinical Neurosciences, Milan, Italy, [7]Università Vita-Salute San Raffaele, Neuroradiology, Milan, Italy

Background and aims: To assess the structural neural correlates of cognitive and behavioral impairment in motor neuron disease (MND).

Methods: 101 patients with sporadic MND (56 classic amyotrophic lateral sclerosis, 31 predominantly upper MND, and 14 predominantly lower MND) and 51 controls were enrolled. Patients were classified into MND with a pure motor syndrome (MND-motor) and with cognitive/behavioural symptoms (MND-plus). Cortical thickness measures and diffusion tensor (DT) metrics of WM tracts were assessed. A Random Forest (RF) approach explored the independent role of cortical and WM abnormalities in explaining major cognitive and behavioral symptoms.

Results: There were 48 MND-motor and 53 MND-plus patients. Relative to controls, both patient groups showed distributed cortical thinning of the bilateral precentral gyrus, cingulate cortex, and frontotemporal regions. In all regions, there was a trend towards a more severe involvement in MND-plus cases, particularly in the temporal lobes. Both patient groups showed a damage of the motor callosal fibers, which was greater in MND-plus. MND-plus patients showed a severe involvement of the extra-motor WM tracts. According to RF, the best predictors of executive and non-executive deficits and behavioural symptoms in MND were the DT MRI metrics of frontotemporal tracts.

Conclusion: Cortical thinning and WM degeneration are highly dependent upon neuropsychological and behavioural symptoms in patients with MND. WM tract damage contributes to the severity of selective cognitive and behavioural manifestations more than cortical thinning.

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P4125

MRI as biomarker in G-CSF mediated clinical ALS stabilization

D. Baldaranov[1], A. Khomenko[1], J. Blume[1], J. Kassubek[2], H.-P. Müller[2], S. Johannesen[1], I. Kobor[1], J. Grassinger[3], T. Bruun[1], G. Schuierer[4], W. Schulte-Mattler[1], A. Schneider[5], M. Deppe[6], U. Bogdahn[1]

[1]University of Regensburg, Neurology, Regensburg, Germany, [2]University of Ulm, Neurology, Ulm, Germany, [3]University of Regensburg, Hematology and Oncology, Regensburg, Germany, [4]University of Regensburg, Neuroradiology, Regensburg, Germany, [5]Sygnis, Heidelberg, Germany, [6]University of Muenster, Neurology, Muenster, Germany

Background and aims: G-CSF (Granulocyte Colony Stimulating Factor) may modulate clinical progression of patients with motor neuron disease. To elucidate potential mechanisms of action long term individual follow-up DTI (diffusion tensor imaging) was applied in ALS patients treated with G-CSF in an open label compassionate use program.

Methods: 23 patients (15 male, 8 female, mean age 51,4) received individual G-CSF long-term continuous treatment up to 48 months in outpatient regimens after informed consent. To prove safety and feasibility, DTI and other clinical biomarkers were prospectively obtained every 3 months. Between 2 and 16 image-datasets per patient were obtained and retrospectively analyzed, two consecutive 1.5 Tesla Siemens scanners were employed. Results were referenced to neurophysiological i-MUNIX (improved Motor Unit Number Index), hematological and clinical (ALS-FRS-r) parameters.

Results: Decreased FA (Fractional Anisotropy) in the corticospinal tract and frontal white matter are consistent with Braak's ALS stages: clinical progression correlates with bilateral axonal integrity of fimbria fornix ($p<0.01$) as hippocampal connectivity. There was a trend in correlating FA data to clinical progression and a significant correlation to i-MUNIX ($p<0.038$) as marker of lower motor neuron function.

Conclusion: FA is a promising biomarker in ALS: it is helpful in staging, evaluation of clinical progression, treatment efficacy, safety, as well as in understanding G-CSF's mode of action. FA - unaffected by individual pathophysiology - needs to be validated as a robust independent biomarker to help accelerate clinical trials in ALS.

Disclosure: Nothing to disclose

P4126

A new therapeutic approach for amyotrophic lateral sclerosis: iPSC-derived CD15+CXCR4+VLA4+ neural stem cell transplantation

S. Brajkovic, C. Simone, M. Nizzardo, F. Rizzo, M. Bucchia, A. Ramirez, N. Bresolin, G.P. Comi, S. Corti
IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy., Milan, Italy

Background and aims: Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by the selective loss of motor neurons. No effective therapies are available. The transplantation of iPSC-derived neural stem cells (NCS) in ALS mice resulted in a significant improvement of the disease phenotype (Nizzardo et al., 2014). In this study, we identified a novel subpopulation of NSCs that displays an increased ability to engraft central nervous system (CNS).

Methods: We differentiated iPS cells from human somatic cells through a non-viral non-integrating protocol of transfection and we directed iPSCs fate into NSCs. Preliminary injections were performed in pups in order to optimize the protocol of injection. The isolation of CD15+CXCR4+VLA4+ NSC subpopulation was obtained by FACS selection. The phenotype of these cells was assessed by morphologic, gene expression, and protein profile analyses. iPSC-purified NSCs were administered by intrathecal injections into SOD1G93A mice and neuropathological assays and functional tests were performed to evaluate any modifications of disease hallmarks.

Results: CD15+CXCR4+VLA4+ NSCs were demonstrated to proliferate and differentiate into the three neuroectodermal lineages, both in vitro and in vivo. We analyzed their ability to migrate into the CNS after minimally invasive injection, and to engraft into the host spinal cord. Transplanted NSCs migrated into the CNS and differentiated into the three neuroectodermal lineages.

Conclusion: Our study showed a significant enhanced survival of host motor neurons after iPSC-derived NSC transplantation by reducing macrogliosis. Finally, we can suggest that the selection of NSC subpopulations can contribute to the development of promising cell-based therapies for ALS and other neurodegenerative disorders.

Disclosure: Nothing to disclose

P4127

Extrapyramidal signs in amyotrophic lateral sclerosis: EXTRALS study

A. Calvo, F. Dematteis, S. Cammarosano, C. Moglia, C.A. Artusi, A. Romagnolo, S. Angrisano, A. Bernardini, A. Ilardi, L. Lopiano, A. Chiò, M.G. Rizzone
University of Torino, ,Rita Levi Montalcini' Department of Neuroscience, Turin, Italy

Background: Recent data suggested that different phenotypic expression in ALS patients, in particular the presence of frontotemporal, parkinsonian and psychiatric symptoms, may represent the manifestation of a spectrum of diseases.

Objectives To determine the presence of extrapyramidal signs in a prospective series of ALS patients.

Methods: 112 consecutive patients with a diagnosis of ALS (July 2012-December 2013) at Torino ALS centre according to El Escorial-Rev criteria were included (58 M, 35 F; mean age 66 years). To detect the presence of extrapyramidal signs, all patients were evaluated by neurologists expert in movement disorders and scored by MDS-UPDRS. Patients with parkinsonian signs underwent 123I-Ioflupane SPECT, genetic analysis for SNCA, parkin, PINK1, DJ-1, LRRK2 and GBA genes.

Results: At baseline 26 patients (9 classic, 10 bulbar, 4 flail leg, 2 flail arm, 1 upper motor neuron) showed parkinsonian signs (UPDRS I mean score 13.0, UPDRS II mean score 18.3, UPDRS III mean score 39.2). Bradykinesia was present in 100%, rigidity in 78.5%, rest tremor in 18.0%, postural tremor in 35.7%, kinetic tremor in 32.0%, gait disturbances in 82.0% and postural instability in 50.0%. 20 patients underwent 123I-Ioflupane SPECT. Only 3 patients showed a reduction of putaminal dopamine transporter binding. A mutation in LRRK2 gen was found in one patient.

Conclusion: Presence of extrapyramidal signs in ALS patients is a frequent clinical feature. Despite a relevant percentage of new diagnosed ALS patients showed parkinsonian signs (28.0%), a nigrostriatal damage was observed only in a low percentage (13.6%) of patients who underwent 123I-Ioflupane SPECT.

Disclosure: Nothing to disclose

P4128

Amyotrophic lateral sclerosis with cognitive Impairment: a role for cognitive reserve?

A. Canosa[1], M. Pagani[2], A. Calvo[1], A. Ilardi[1], A. Montuschi[1], B. Iazzolino[1], M. Barberis[3], M. Brunetti[3], G. Restagno[4], A. Chio[1]

[1]University of Torino, Turin, Italy, [2]CNR Rome, Rome, Italy, [3]Univ of Torino, Turin, Italy, [4]AOU Città della Salute e della Scienza, Turin, Italy

Background and aims: 50% of ALS cases display cognitive decline, from frontotemporal dementia (ALS-FTD), to executive (ALS-ECI), non-executive (ALS-NECI) and behavioral impairment (ALS-Bi). A protective role of cognitive reserve (CR) is known in Alzheimer's disease (AD) and FTD. We aimed to verify the CR hypothesis in ALS-related cognitive impairment.

Methods: Our discovery cohort (DC) included 183 incident cases from Piemonte (January 2009 - December 2011). A validation cohort (VC) (n=113) included patients from other regions diagnosed in such period and incident cases from Piemonte (January 2012 - June 2013). Patients underwent neuropsychological and genetic testing. In the DC 49.7% were cognitively normal, 12.6% ALS-FTD, 19.7% ALS-ECI, 5.5% ALS-NECI, 6.0% ALS-Bi, 6.0% non-classifiable (ALS-NCCI). In the VC 50.5% were cognitively normal, 15.9% ALS-FTD, 18.6% ALS-ECI, 3.5% ALS-NECI, 6.2% ALS-Bi, 5.3% ALS-NCCI. A Reserve Index (RI) (2-12) was calculated from education and occupation.

Results: In the DC ALS-FTD patients showed lower education (4.7 years, SD 1.9) and RI (4.9, SD 1.3) than other groups (p=0.0001). In the VC ALS-FTD patients (7.0 years, SD 2.6) had the same education of ALS-NECI (7.0, SD 1.4), that was lower than other categories (p=0.003). ALS-FTD patients had lower RI (5.7, SD 1.6) than other groups but ALS-NECI (p=0.003). Results were confirmed among c9orf72 mutation carriers (p=0.012). TMT B, TMT B-A, Stroop Colour-Word Interference Test, WAIS-R Block Design, WMS-R-Form 2, FAB (p=0.0001) and CPM total score (p=0.001) were related to RI.

Conclusion: CR may have a role in ALS-related cognitive impairment, primarily frank FTD, including c9orf72 mutation carriers, mainly due to frontal dysfunction.

Disclosure: Nothing to disclose

P4129

Altered secretion of exosomes by muscle cells: role in ALS pathogenesis

S. Duguez[1], L. Le Gall[1], W.J. Duddy[1], C. Martinat[2], M. Thorley[1], G. Ouandaogo[1], J.P. Loeffler[3], J.-L. Gonzales De Aguilar[3], G. Butler Brown[1], V. Mouly[1], P.F. Pradat[4]

[1]Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS974, CNRS FRE3617, Center for research in Myology, Paris, France, [2]INSERM/UEVE UMR 861, I-STEM, AFM, Evry, France, [3]Université de Strasbourg / INSERM U1118, Mécanismes Centraux et Périphériques de la Neurodégénérescence, Strasbourg, France, [4]Departement des Maladies du Systeme Nerveux, AP-HP Pitié Salpétrière, Paris, France

Background and aims: The potential involvement of exosome trafficking is implicated in ALS by the aggregation of lysosomally-directed proteins in the cytosol of patient cells (both sporadic and familial cases), and by mutations in genes involved in autophagy and multivesicular biogenesis pathways in familial cases. Exosomes are small vesicles shown to export functional proteins, mRNA and miRNA from different cell types including muscle cells. Several studies suggest an involvement of skeletal muscle in ALS. Our purpose was to determine whether exosome secretion is altered in ALS muscle cells, and could alter the intercellular communication between muscle and nerves.

Methods: To explore disruption of vesicle trafficking and secretion in ALS muscle, immunostains, Western blots, and RTq-PCR were performed on samples from sporadic ALS patients and aged-matched healthy subjects (n=10/group). Transcriptomic analysis was carried out for secretome prediction and gene set enrichment.

Results: We observed a consistently striking and previously unnoticed accumulation of exosomal vesicles in patient myotubes, and confirmed this in vivo on muscle biopsies from sporadic ALS patients. In silico secretome prediction suggested a mechanistic basis of this, showing a significant enrichment in both endosomal and lysosomal compartments, indicating disruption of exosome genesis and secretion, which was consistent with gene set enrichment analysis showing disrupted vesicle trafficking.

Conclusion: We hypothesise that altered exosome secretion influences the intercellular communication between the muscle and its environment, including motor neurons. This phenomenon occurs independently of muscle denervation and could be a key element in the disease progression.

Disclosure: This work was financed by INSERM and Direction Generale de l'Organisation des Soins (DGOS), and by the Association Française contre les myopathies (AFM).

P4130

Quantifying spinal cord atrophy: an MRI tool to investigate the selectivity of muscle weakness in SMA

M.-M. El Mendili[1], T. Lenglet[2], S. Lehericy[3], H. Benali[1], P.F. Pradat[4]

[1]Sorbonne Universités, UPMC Univ Paris 06, UM CR 2, CNRS UMR 7371, INSERM U 1146, Laboratoire d'Imagerie Biomédicale, Paris, France, [2]Pitié-Salpêtrière Hospital, Service Explorations Fonctionnelle Neurologie, Paris, France, [3]Pitié-Salpêtrière Hospital, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, INSERM UMRS_1127, Paris Cedex 13, France 75651; Pitié-Salpêtrière Hospital, Centre de Neuroimagerie de Recherche, Paris Cedex 13, France 75651., Paris, France, [4]Departement des Maladies du Systeme Nerveux, AP-HP Pitié Salpétrière, Paris, France

Background and aims: Spinal muscular atrophy (SMA) is characterized by lower motor neuron (LMN) loss that leads to proximal muscle wasting and paralysis. In this study, we investigated the link between spinal cord atrophy profile and the proximal muscles deficits in spinal muscular atrophy.

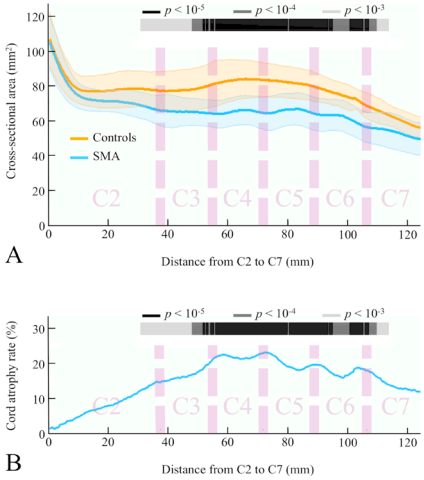
Methods and Materials: 18 patients with type III/V SMN1-linked SMA and 18 age-matched controls were recruited. Patients were scored using manual muscle testing (MMT) (Table 1). Subjects were scanned at 3T MRI system (Tim Trio, Siemens Healthcare). Spinal cord was imaged using a T2-weighted sequence (52 sagittal slices, FOV=280mm, TE/TR=1500/120ms, voxel size = 0.9x0.9x0.9mm3). Data were segmented. Cord cross-sectional area (CSA) was computed along the cervical spinal cord. The difference in CSA between SMA patients and controls was assessed using permutation test (one side). Spearman's rank correlation coefficient was used to investigate correlations between CSA and MMT. A supra-significance level alpha=10-3 was used.

Table 1. Population demographics and clinical futures in SMA patients.

Characteristics	SMA patients	Controls
Number	18	18
Age	37 ± 11 years	35 ± 11 years
Gender	9F:9M	11F:7M
Type	3IV, 11IIIb, 4IIIa	–
Disease duration	26 ± 15 years	–
MMT		
Arm (/70)	56.28 ± 10.17	–
Leg (/70)	46.67 ± 15.23	–
Total (/140)	102.94 ± 24.07	–
Proximal muscles		
C5 (%)	73.33 ± 19.40	–
C6 (%)	84.72 ± 17.10	–
Distal muscles		
C7 (%)	87.78 ± 15.92	–
C8 (%)	72.22 ± 13.53	–

Results: CSA showed a significant atrophy gradient mainly located between C3 and C6 vertebral levels with a cord atrophy rate ranging from 5.4% to 23% (Figure 1). There were no correlations between CSA and MMT nor between CSA and disease duration.

Figure 1. (A) Cross-sectional area profile in SMA patients and controls. (B) Cord atrophy rate in SMA patients.



Conclusion: Atrophy predominates in the spinal segments innervating the proximal muscles. The missing correlations between CSA and MMT as well as the clear distal deficit showed by MMT in our SMA population; suggest that the loss of motor neuron cell bodies may not recapitulate all the mechanisms responsible for clinical deficits.

Disclosure: This study was supported by the Association Française contre les Myopathies (AFM) and the Institut pour la Recherche sur la Moelle épinière et l'Encéphale (IRME). The research leading to these results has also received funding from the program "Investissements d'avenir" ANR-10-IAIHU-06.

Movement disorders 9

P4131

Discriminatory performance of a suspicion index in identifying Niemann-Pick disease Type C among patients with complex early-onset ataxias

M. Synofzik[1], Z. Fleszar[2], L. Schöls[1], J. Müller vom Hagen[2], P. Bauer[3], J.V. Torres Martin[4], S. Kolb[5]

[1]Tübingen, Germany, [2]Hertie-Institute for Clinical Brain Research, University of Tübingen, Department of Neurodegenerative Diseases, Tübingen, Germany, [3]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, [4]Syntax for Science SL, Basel, Switzerland, [5]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Background and aims: Despite recent progress in genetics a notable proportion of patients with early-onset ataxia (EOA: onset <40 years) still remain without molecular diagnosis, which highlights the need for easily applicable clinical tools to identify treatable cases among subjects with unexplained EOA. Niemann-Pick disease type C (NP-C) suspicion index (SI) helps to identify NP-C in patients with unexplained neurological disease, but its discriminatory performance in EOA has been questioned. We evaluated the ability of the NPC-SI to discriminate between EOA cases with confirmed NP-C (n=53) and EOA cases (n=86) negative for NP-C mutations.

Methods: NP-C signs and symptoms were compared between both groups by systematic phenotyping according to the SI protocol (Wijburg et al, Neurology 2012;78:1–1). NP-C SI risk prediction scores (RPS) were calculated for all patients and SI discriminatory performance was evaluated.

Results: Of the most frequent NP-C signs/symptoms, vertical supranuclear gaze palsy, cognitive impairment, splenomegaly and dystonia were less frequent in non-NP-C EOA cases vs. NP-C EOA cases (Fig. 1). Dysarthria/dysphagia was observed at a similar frequency in both groups. Spasticity was more frequent in non-NP-C EOA cases. Although moderate (40–69 points) and high (≥70 points) RPS were seen in 16/86 (19%) and 8/86 (9%) non-NP-C EOA cases (Fig. 2), the SI had excellent discriminatory power (AUC 0.980). Discriminatory performance was not affected by patient age.

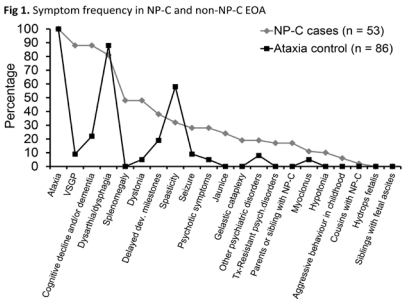


Fig 1. Symptom frequency in NP-C and non-NP-C EOA

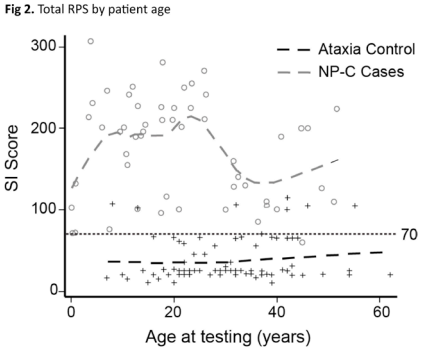


Fig 2. Total RPS by patient age

Conclusion: The NP-C SI distinguished well between NP-C and non-NPC EOA cases, is easy to apply, and will reliably aid identification/diagnostics of patients with complex EOAs who warrant further investigation for NP-C.

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P4132

Deep brain stimulation can preserve working abilities in Parkinson's disease

N. Kovacs[1], I. Balás[2], S. Komoly[2], T. Dóczi[1], J. Janszky[1], Z. Aschermann[2], A. Makkos[2], G. Deli[2]
[1]MTA-PTE Clinical Neuroimaging MR Research Group, Pécs, Hungary, [2]University of Pécs, Pécs, Hungary

Background and aims: There is a debate on the potential advantageous effects of bilateral subthalamic deep brain stimulation (DBS) in the treatment of Parkinson's disease with early fluctuations. Our investigation aimed to evaluate if DBS therapy was able to preserve the working capabilities.

Methods: We reviewed the data of 40 young (<60 year-old) PD patients who underwent DBS implantation at University of Pécs and had an at least 2 years follow-up. Patients were categorized into two groups based on their working capabilities at time of surgery: 'Active job' group (n=20) and 'No job' group (n=20). Baseline characteristics were comparable. Severity of motor symptoms (UPDRS-3), quality of life (EQ-5D) and presence of active job were evaluated preoperatively and 2 years postoperatively.

Results: Although similar (approximately 50%) improvement was achieved in the severity of motor and major non-motor symptoms in both groups, the postoperative quality of life was significantly better in the 'Active job' group (0.687 vs. 0.587, medians, $p<0.05$). Majority (80%) of 'Active job' group members were able to preserve their job 2 years after the operation. However, only a minimal portion (5%) of the 'No job' group members was able to return to the world of active employees ($p<0,01$).

Conclusion: Although our study has several limitations, our results fits well with the conclusions of EarlyStim study. In patients with active job the appropriately 'early' usage of DBS might help preserve working abilities in a two-year time-frame and gain higher improvement in quality of life.

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P4133

Presenting symptoms of GBA-related Parkinson's disease

N.D. Kresojevic[1], M. Janković[1], I. Petrović[1], K. Kumar[2], N. Dragasevic[1], V. Dobricic[1], I. Novakovic[1], M. Svetel[1], C. Klein[3], T. Pekmezovic[4], V. Kostic[1]
[1]Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia, Belgrade, Serbia, [2]Kolling Institute of Medical Research, Royal North Shore Hospital, University of Sydney, Department of Neurogentics, Sidney, Australia, [3]University of Lübeck, Institute of Neurogenetics, Lübeck, Germany, [4]Clinic of neurology, Neuroepidemiology, Belgrade, Serbia

Background and aims: Mutations in the Glucocerebrosidase gene (GBA) are associated with Parkinson's disease (PD). It has been shown that GBA-related PD (PD-GBA) patients had an earlier age at PD onset and more prevalent non-motor symptoms when compared to "sporadic" PD patients without such mutations (sPD). Aim of our research was to explore whether presenting symptoms differ between PD-GBA and sPD patients.

Methods: Demographic and clinical features (including presenting symptoms) were collected for 578 PD patients. Sequence analysis was performed for exons 8-11 of the GBA gene for all participants.

Results: 39 PD patients (6.7%) with GBA mutations were compared to 539 PD patients without them. No statistically significant differences were found regarding presenting symptoms (bradykinesia, rigidity, tremor, writing difficulties, gait problems) with the exception of pain which was more frequently reported in the PD-GBA (10.3%; all with severe mutation) than in the sPD group (3.0%) ($p=0.039$).

Conclusion: PD patients with severe GBA mutations might have more frequently pain as a presenting symptom when compared with PD patients without such mutations.

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P4134

Evaluating the efficacy and safety of opicapone in patients over 70 years with Parkinson's disease and motor fluctuations

A. Lees[1], J. Ferreira[2], N. Lopes[3], R. Costa[3], A. Santos[3], C. Oliveira[3], R. Pinto[3], T. Nunes[3], J.F. Rocha[3], P. Soares-da-silva[3]

[1]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [2]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [3]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal

Background and aims: Opicapone (OPC) is a novel once-daily peripheral COMT inhibitor shown to be safe and effective in reducing OFF-time in Parkinson's disease (PD) patients with motor fluctuations. PD mainly affects the elderly and the incidence increases with age, being the second most prevalent neurodegenerative disease among older subjects.

Methods: Data from two multicentre, double-blind, randomised, placebo- and active-controlled studies (BIPARK I and II) was pooled and evaluated by age (<70 and ≥70 years). Efficacy outcome measures included the change from baseline to endpoint in absolute OFF-time and the OFF- and ON-time responder rates (≥1 hour). Safety was evaluated by analysis of reported adverse events (AEs).

Results: 221 patients ≥70 years were included in the analysis (N=69, 66 and 86 for placebo, 25mg- and 50mg-OPC, respectively). Mean daily OFF-time decreased by 1.41h for placebo, 1.77h (p=0.4086) for 25mg-OPC and -2.26h (p=0.0384) for 50mg-OPC. Consistently, a higher proportion of patients receiving either 25mg- or 50mg-OPC achieved the OFF- and ON-time responders endpoint ($p<0.05$ for 50mg-OPC). AEs occurring more frequently in the elderly (adjusted for placebo) included hallucinations (4.6% vs. 0.1%), visual hallucinations (3.8% vs. 0.1%) and weight decreased (4.6% vs. 1.1%). The incidence of serious AEs was lower in OPC treated patients than placebo.

Conclusion: OPC is effective and well tolerated by PD patients over 70 years old.

Disclosure: Nothing to disclose

P4135

Safety of opicapone in patients with Parkinson's disease and motor fluctuations: 1-year follow-up

A. Lees[1], J. Ferreira[2], R. Costa[3], C. Oliveira[3], R. Pinto[3], N. Lopes[3], T. Nunes[3], J.F. Rocha[3], P. Soares-da-silva[3]

[1]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [2]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [3]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal

Background and aims: Opicapone (OPC) is a novel once-daily peripheral COMT-inhibitor shown to be safe and effective in reducing OFF-time in Parkinson's disease (PD) patients with motor fluctuations. The aim of this study was to evaluate the safety of OPC as add-on to levodopa over 1-year of treatment.

Methods: Subjects that completed the double-blind (DB) part of a randomized, placebo-controlled study (BIPARK II) were enrolled into an open-label 1-year extension. Subjects started with 25mg-OPC irrespective of prior DB treatment. One week after, either OPC (25 or 50mg), levodopa or anti-PD drugs could be adjusted based on individual response. Safety was assessed by adverse events (AEs), laboratory, vital-signs, ECG, physical and neurological examinations, modified Minnesota Impulsive Disorders Interview (mMIDI) and Columbia Suicide Severity Rating Scale (C-SSRS).

Results: 286 (81%) subjects completed the 1-year treatment. The most commonly reported AEs were dyskinesia (21.5%), (worsening) PD (17.0%), falls (9.1%), blood CPK increased (7.4%), insomnia (5.7%) and orthostatic hypotension (5.4%). The majority of AEs were mild to moderate in intensity. Serious AEs were reported for 11.3% of the patients. Five deaths occurred, all but one (cerebral hemorrhage after traumatic brain injury) were considered unrelated to treatment. There were no reports of urine discoloration, severe diarrhea, myocardial infarction, prostate cancer or any serious hepatic event. Melanoma was confirmed in 1 patient. C-SSRS showed no effect on suicidality. Impulsive disorders, as screened by mMIDI, were reported in few subjects (4.0%).

Conclusion: OPC long-term use was safe and well tolerated.

Disclosure: Nothing to disclose

P4136

Evaluation of hepatic safety of opicapone in patients with Parkinson's disease

N. Lopes[1], J. Ferreira[2], A. Lees[3], H. Gama[1], A. Santos[1], C. Oliveira[1], R. Costa[1], T. Nunes[1], J.F. Rocha[1], P. Soares-da-Silva[1]

[1]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal, [2]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [3]National Hospital for Neurology and Neurosurgery, London, United Kingdom

Background and aims: Opicapone (OPC) is a novel once-daily peripheral COMT-inhibitor shown to be safe and effective in reducing OFF-time in Parkinson's disease (PD) patients with motor fluctuations. Here we evaluate the effects of OPC on hepatobiliary function.

Methods: The safety data of 2 multicentre, double-blind, randomised, placebo- and active-controlled studies (BIPARK I and II) was pooled. Hepatic-related adverse events and changes from baseline in hepatic laboratory parameters were evaluated.

Results: A total of 509 subjects treated with OPC (25 or 50mg) and 257 with placebo were analyzed. No relevant changes from baseline to endpoint in mean values for hepatic laboratory parameters in any treatment group were observed. The incidence of potential clinically important values (alanine aminotransferase ≥ 3xULN, aspartate aminotransferase ≥ 3xULN, total bilirubin ≥ 2xULN, alkaline phosphatase ≥ 1.5xULN) was similar for placebo and OPC groups. Hepatic-related adverse events were reported by 2.0% of patients in OPC groups compared to 3.5% in placebo. There were no cases of potential Hy's law, hepatitis, hepatic failure or other severe hepatic injuries reported in OPC groups.

Conclusion: OPC was not associated with clinically relevant effects on hepatobiliary function.

Disclosure: Nothing to disclose

P4137

Efficacy of opicapone in combination with dopamine agonists or MAO-B inhibitors on the treatment of motor fluctuations in Parkinson's disease.

N. Lopes[1], J. Ferreira[2], A. Lees[3], R. Costa[1], A. Santos[1], C. Oliveira[1], R. Pinto[1], T. Nunes[1], J.F. Rocha[1], P. Soares-da-Silva[1]

[1]BIAL – Portela & C[a] – S.A., Dept. R&D, S. Mamede do Coronado, Portugal, [2]Instituto de Medicina Molecular, Neurological Clinical Research Unit, Lisbon, Portugal, [3]National Hospital for Neurology and Neurosurgery, London, United Kingdom

Background and aims: Opicapone (OPC) is a novel once-daily peripheral COMT inhibitor shown to be safe and effective in reducing OFF-time in Parkinson's disease (PD) patients with motor fluctuations. PD patients are commonly treated with dopamine agonists (DA) or MAO-B inhibitors (MAO-Bi) in association with levodopa.

Methods: Data from two multicentre, double-blind, randomised, placebo- and active-controlled studies (BIPARK I and II) was pooled and analyzed by concurrent use of DA or MAO-Bi at baseline (yes/no). Efficacy outcome measures included the change from baseline to endpoint in absolute OFF-time and the OFF- and ON-time responder rates (≥1 hour).

Results: 521 (69%) patients were using DA (N=185, 158 and 178 for placebo, 25mg- and 50mg-OPC, respectively) and 151 (20%) were using MAO-Bi (N=49, 46 and 56, for placebo, 25mg- and 50mg-OPC, respectively). The mean placebo-adjusted OFF-time reduction was -35.5 min (p=0.0329) and -25.7 min (p=0.4120) for 25mg-OPC plus DA or MAO-Bi, respectively; -54.6 min (p=0.0007) and 63.7 min (p=0.0326) for 50mg-OPC plus DA or MAO-Bi, respectively. Consistently, a higher proportion of patients receiving either 25mg- or 50mg-OPC achieved the OFF- and ON-time responders endpoint ($p<0.05$ for 50mg-OPC).

Conclusion: OPC was effective in reducing OFF-time regardless the concomitant use of DA or MAO-Bi.

Disclosure: Nothing to disclose

P4138

First-time deep brain stimulation of ventral and dorsal parts of the substantia nigra and its therapeutic effect on axial motor symptoms in Parkinson's disease: a case report.

P. Ludewig[1], C. Moll[2], A. Gulberti[2], U. Hidding[1], J. Koeppen[3], W. Hamel[3], C. Gerloff[1], C. Buhmann[1], M. Poetter-Nerger[1], M. Geldesblom[1]

[1]*Universitätsklinikum Hamburg-Eppendorf, Neurology, Hamburg, Germany,* [2]*Universitätsklinikum Hamburg-Eppendorf, Neurophysiology, Hamburg, Germany,* [3]*Universitätsklinikum Hamburg-Eppendorf, Neurosurgery, Hamburg, Germany*

Background and aims: Therapeutic options of axial motor impairment in Parkinson's disease are limited due to variable treatment success rates of drugs and deep brain stimulation (DBS). Recently, positive effects of simultaneous stimulation of the substantia nigra (SNr) und nucleus subthalamicus (STN) on „freezing of gait" (FOG) were reported (Weiss,Walach et al. 2013). It is unknown which parts of the SNr are relevant for gait disturbances. We present a case report of a Parkinson's patient with DBS stimulated at different heights in the SNr. We aimed to investigate whether ventral stimulation of the SNr might be beneficial for gait disturbances in Parkinson's disease.

Case Report: A 68-year-old patient with preoperative FOG underwent DBS with deep implantation of 8-pole electrodes covering different region of the SNr with four contacts. 12 months after operation, we evaluated the effect of of nigral stimulation at each contact (1.5mA, 119Hz, 60µs) in combination with a standard STN stimulation (monopolar stimulation, 119Hz, 60µs). Outcome measures included changes in the MDS-UPDRS Scores, FOG Score, Berg-Balance-Score, and neuropsychiatric side effects.

Results: Whereas stimulation in the STN improved all scores, additional ventral or dorsal SNr stimulation did not improve scores beyond the effects STN stimulation. However, severe neuropsychiatric adverse effects occurred resulting in the abortion of chronic stimulation of the ventral parts of the SNr.

Conclusion: This is the first report of deep brain stimulation in different parts of the SNr. We did not observe beneficial effects on axial motor symptoms in Parkinson's disease, but severe neuropsychiatric side effects, which have not been reported before.

Disclosure: Nothing to disclose

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P4139

Exposure-response analyses of CD56bright NK cell expansion and regulatory T-cells reduction by daclizumab high-yield process (HYP) in subjects with multiple sclerosis

L. Diao[1], Y. Hang[1], A.A. Othman[2], D. Mehta[1], L. Amaravadi[1], I. Nestorov[1], J. Tran[1]
[1]Biogen Idec, Cambridge, MA, USA, [2]AbbVie, North Chicago, IL, USA

Background and aims: Daclizumab HYP is a humanized IgG1 monoclonal antibody specific for CD25, the high-affinity interleukin 2 receptor alpha subunit. In registration studies in subjects with relapsing-remitting multiple sclerosis (RRMS), daclizumab HYP demonstrated efficacy on clinical endpoints and resulted in expansion of CD56bright natural killer (NK) cells and reduction of regulatory T-cells (Tregs). This analysis characterized the quantitative relationship between daclizumab HYP exposure and biomarker effects.

Methods: More than 7000 observations for each biomarker from 1400 subjects with RRMS in SELECT/SELECTION, OBSERVE and DECIDE studies were included in the analyses using non-linear mixed-effects modelling.

Results: CD56bright NK cell expansion was characterized by an indirect response model with daclizumab HYP stimulating the zero-order rate constant (Kin) for the increase in cell number. Estimated maximum expansion ratio of CD56bright NK cells induced by daclizumab HYP treatment was ~5 with an EC50 of 18.0μg/mL. After the last dose at steady state, CD56bright NK cells returned to baseline levels within 24 weeks. Daclizumab HYP induced reduction of Tregs was characterized by a direct Emax model. Estimated maximum Treg decline was ~60% with IC50 value 3.97μg/mL and a Hill coefficient of 2. After the last dose at steady-state, Tregs returned to baseline levels in approximately 20 weeks.

Conclusion: The developed models quantitatively characterized the relationship between daclizumab HYP exposure and magnitude/time course of its effects on CD56bright NK cells and Tregs. Effects of daclizumab HYP on these two biomarkers at clinically efficacious exposures were significant and reversible in parallel with daclizumab HYP clearance from the body.

Disclosure: Studies supported by Biogen Idec and AbbVie Biotherapeutics Inc.

P4140

Population pharmacokinetics of daclizumab high-yield process (HYP) in subjects with multiple sclerosis

L. Diao[1], Y. Hang[1], A.A. Othman[2], I. Nestorov[1], J. Tran[1]
[1]Biogen Idec, Cambridge, MA, USA, [2]AbbVie, North Chicago, IL, USA

Background and aims: In Phase 2 and 3 trials, daclizumab HYP demonstrated efficacy in reducing disease activity in relapsing-remitting multiple sclerosis (RRMS). This analysis characterized the population pharmacokinetics for daclizumab HYP and identified factors correlating with exposures using combined data from Phase 1–3 studies in healthy subjects and MS patients.

Methods: Daclizumab HYP measurable serum concentrations (n=17,139) from 1,670 subjects (71 healthy; 1,599 MS) were analysed using a non-linear mixed-effects modelling approach. Evaluated doses ranged from 50–300mg with subcutaneous and 200–400mg with intravenous administration.

Results: A two-compartment model with first-order absorption and elimination adequately described the pharmacokinetics of daclizumab HYP in healthy volunteers and RRMS patients. Clearance was 0.212 L/day and central volume of distribution was 3.92 L, scaled by body weight, with exponents of 0.87 and 1.12, respectively. Peripheral volume of distribution was 2.42 L. Absorption lag time, mean absorption time, and absolute bioavailability (100–300mg) for subcutaneous administration were 1.61 h, 7.2 days and 88%, respectively. Terminal half-life was 21 days. Body weight explained 37% and 27% of the inter-individual variability for clearance and central volume of distribution, respectively. Neutralizing antibody positive status (0.8% in all pharmacokinetic records) increased the daclizumab HYP clearance by 19%. Daclizumab HYP exposure was not impacted by gender, age, or baseline CD4+CD25+ T-cells.

Conclusion: In subjects with MS, daclizumab HYP is characterized by low clearance, small volume of distribution, and high subcutaneous bioavailability, similar to observations in healthy volunteers. The impact of the covariates on daclizumab HYP pharmacokinetics was not clinically relevant.

Disclosure: Studies supported by Biogen Idec and AbbVie Biotherapeutics Inc.

P4141

Impact of early treatment of MS with interferon beta-1b: Patient-reported outcomes at the 11-year follow-up of BENEFIT (BENEFIT 11)

G. Edan[1], M. Freedman[2], X. Montalban[3], H.-P. Hartung[4], B. Hemmer[5], E. Fox[6], F. Barkhof[7], S. Schippling[8], I.-K. Penner[9], F. Foley[10], A. Schulze[11], D. Pleimes[12], C. Pohl[13], R. Sandbrink[14], G. Suarez[15], E.-M. Wicklein[16], L. Kappos[17]

[1]CHU-Hopital Pontchaillou, Rennes, France, [2]University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Canada, [3]Department of Neurology-Neuroimmunology, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Heinrich-Heine Universität, Neurology, Düsseldorf, Germany, [5]Technische Universität München and Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [6]University of Texas Medical Branch, Austin, USA, [7]VU University Medical Center, Amsterdam, The Netherlands, [8]University Hospital Zurich, Zurich, Switzerland, [9]University of Basel and University Hospital Basel, Basel, Switzerland, [10]Yeshiva University, School of Psychology, New York, USA, [11]PAREXEL International, Berlin, Germany, [12]Myelo Therapeutics GmbH, Berlin, Germany, [13]Bayer Pharma AG and University Hospital of Bonn, Berlin, Germany, [14]Bayer Pharma AG and Heinrich-Heine Universität, Berlin, Germany, [15]Bayer HealthCare Pharmaceuticals, Whippany, USA, [16]Bayer Pharma AG, Berlin, Germany, [17]University Hospital Basel, Basel, Switzerland

Background and aims: Long-term follow up in the BENEFIT trial showed that patients treated with interferon beta-1b immediately after CIS had significantly better clinical and MRI outcomes compared with delayed treatment. Data on patient-reported outcomes (PROs) will further describe the impact of early treatment on long-term quality of life (QoL) for these patients.

Methods: Patients with CIS were randomly assigned to receive interferon beta-1b 250 μg (early treatment) or placebo (delayed treatment). After 2 years or conversion to CDMS, patients receiving placebo were offered active treatment. Eleven years after the initial randomization, all patients from participating study centers were approached to complete a comprehensive reassessment, including EQ-5D, FAMS, CES-D, and FSMC.

Results: 278 patients (of the original 468) were enrolled (71.3% of patients from sites participating in BENEFIT11). At Year 11, median EDSS was 2.0 in both treatment arms. Results from both arms combined showed (median [Q1, Q3]): EQ-5D VAS change from baseline score, 0.0 (-10.0, 8.0); EQ-5D HRQoL change from baseline score, 0.00 (-0.19, 0.02); FAMS TOI, 117.10 (92.85, 134.00); CES-D total score, 9.00 (4.00, 19.00); and FSMC total score, 45.00 (26.00, 66.00). 143/278 patients (51.4%) reported fatigue (defined as FSMC total score >42) and 84/278 patients (30.2%) reported depressive symptoms (defined as >15 on CES-D). There was little difference between the two treatment arms for these variables.

Conclusion: Measures of QoL over 11 years remained stable and may reflect the beneficial impact of treatment early in the disease on the clinical course of MS.

Disclosure: Study supported by Bayer HealthCare Pharmaceuticals

P4142

Abstract cancelled

P4143

Systemically administered exosomes mediate recovery in the Theiler's Mourine Ecephalomyelitis Virus animal model of multiple sclerosis.

J. Ramos Cejudo[1], M. Fernandez-Fournier[1], M. Gutierrez-Fernandez[2], B. Rodriguez-Frutos[2], L. Otero-Ortega[2], C. Guaza[3], T. Navarro[4], S. Cerdan[4], E. Díez-Tejedor[5]
[1]Madrid, Spain, [2]IdiPAZ, La Paz University Hospital, Neuroscience Labarotary, Madrid, Spain, [3]Cajal Research Institute, Neuroimmunology, Madrid, Spain, [4]Alberto Sols Biomedical Research Institute, Imaging, Madrid, Spain, [5]Hospital Universitario la Paz, Neurology department and Stroke centerdepartment and Stroke center, Madrid, Spain

Background and aims: Exosomes (EXO) are small vesicles of 40 to 150nm released by different cell types, mediating intercellular communication. An animal model that has recently gained relevance in the study of Multiple Sclerosis is Theiler's Mourine Encephalomyelitis Virus (TMEV). We aimed to study if the administration of exosomes derived from mesenchymal stem cells could mediate recovery in the TMEV model.

Methods: Exosomes purified from human adipose tissuederive mesenchymal stem cells were intravenously administered (25ug/Kg,i.v.) to mice undergoing demyelinating disease induced by TMEV injection (2x10^6 viral units) at Cajal Institute, Madrid. Animals, n=27 were randomly divided into 3 groups (Sham, n=7; TMEV, n=10; TMEV-EXO, n=10). Animals were evaluated clinically and by Magnetic Resonance Imaging (MRI).

Results: Fifteen days post-exosome administration motor activity and memory improved in treated animals; and 7-tesla MRI analysis showed partial resolution of both brain connectivity and ventricular atrophy. Myelin basic protein staining in vehicle treated mice showed higher demyelination in subcortical white matter and KI-67 cell proliferation and the levels of Oligodendrocyte precursors' markers PDGFR and CC1 were higher in the Subventricular Zone of TMEV-EXO animals. Proteomic content of exosomes in cell supernants was analyzed by Orbitrap identifying over 1,300 proteins, including a number of trophic factors and signaling molecules not previously identified in the literature.

Conclusion: Our results suggest that mesenchymal stem cells derived exosomes have the potential to mediate recovery after central nervous system demyelination and might provide a novel approach to treat autoimmune diseases such as multiple sclerosis.

Disclosure: Nothing to disclose

P4144

"Number Needed to Treat" analysis to assess the comparative outcomes from teriflunomide and dimethyl fumarate studies in relapsing multiple sclerosis

M.S. Freedman[1], X. Montalban[2], A.E. Miller[3], C. Dive-Pouletty[4], T.P. Leist[5]
[1]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, Canada, [2]Department of Neurology-Neuroimmunology, Vall d'Hebron University Hospital, Barcelona, Spain, [3]Icahn School of Medicine at Mount Sinai, New York, USA, [4]Genzyme, a Sanofi company, Chilly-Mazarin, France, [5]Comprehensive Multiple Sclerosis Center, Thomas Jefferson University Hospital, Philadelphia, USA

Background and aims: Teriflunomide and dimethyl fumarate (DMF) have demonstrated efficacy in clinical trials in patients with relapsing-remitting multiple sclerosis. Exploratory analyses of treatment effects can be compared informally using relative reductions in a specific endpoint. The number needed to treat (NNT) to prevent an event was assessed for outcomes in studies with teriflunomide and DMF.

Methods: NNTs were derived using data from studies with teriflunomide (TEMSO, NCT00134563; TOWER, NCT00751881) or DMF (DEFINE, NCT00420212; CONFIRM, NCT00451451) based on the inverse of absolute differences between treatment and placebo groups.

Results: Teriflunomide and DMF significantly reduced risk of relapse (all studies). NNTs to prevent 1 relapse were similar across studies (5.9 [TEMSO], 5.6 [TOWER], 5.3 [DEFINE], 5.6 [CONFIRM]). Risk of disability progression sustained for 12 weeks was significantly reduced in TEMSO, TOWER, and DEFINE but not CONFIRM. Corresponding NNTs to prevent disability progression were 13.8, 17.4, 10.8, and 30.2. Risk of relapse leading to hospitalization was significantly reduced in TEMSO and TOWER but not in DEFINE and CONFIRM. Corresponding NNTs were lower in TEMSO (12.5) and TOWER (20) than in DEFINE (50) and CONFIRM (50). Safety data and corticosteroid use will be presented.

Conclusion: A comparable effect size for teriflunomide and DMF on relapse was demonstrated using the NNT approach. NNTs to prevent disability progression with teriflunomide showed a consistent significant reduction in risk vs placebo in both TEMSO and TOWER, whereas for DMF, comparable NNTs were observed in DEFINE, but not in CONFIRM. Reduction of risk for relapse leading to hospitalization was significant only for teriflunomide.

Disclosure: Study supported by Genzyme, a Sanofi company.

P4145

Do patients with multiple sclerosis understand quantitative health information? Comparison of a natalizumab-treated cohort from the German PERCEPT study with a probabilistic national sample

W. Gaissmaier[1], M. Galesic[2], R. Garcia-Retamero[2], I. Kleiter[3], S. Meuth[4], S. Koepke[5], C. Heesen[6]

[1]Universitaet Konstanz, Fachbereich Psychologie, Sozialpsychologie und Entscheidungsforschung, Konstanz, Germany, [2]Max-Planck-Institut für Bildungsforschung, Berlin, Germany, [3]St. Josef Hospital, Neurologie, Bochum, Germany, [4]Universitaetsklinikum, Klinik für Allgemeine Neurologie und Institut für Physiologie I - Neuropathophysiologie, Muenster, Germany, [5]Universitaetsklinikum Schleswig-Holstein, Forschung und Lehre in der Pflege, Lübeck, Germany, [6]Universitaetsklinikum Hamburg-Eppendorf, MS Day Hospital and Outpatient Unit Institute of Neuroimmunology and Clinical MS Research, Hamburg, Germany

Background and aims: Natalizumab (NAT) is a highly effective therapy in relapsing multiple sclerosis (MS), yet bears the risk of a progressive multifocal leukoencephalopathy as a rare but severe side effect. To understand quantitative information about its benefits and risks and make informed treatment decisions, patients require statistical numeracy. It is unknown, however, whether MS affects numeracy, which is why we compared numeracy between NAT treated MS patients and a probabilistic national sample.

Methods: The prospective, observational, multicentre study PERCEPT investigated NAT patients' and neurologists' benefit/risk perception and knowledge in Germany. Numeracy of NAT patients was assessed as the proportion of correct answers on a standard test (1). Patients (N=344) were compared to published numeracy data from a German probabilistic sample (N=1,001; (1)) with an analysis of variance also including sex, age, and education as predictors.

(1) Galesic M, Garcia-Retamero R. Arch Intern Med. 2010;170(5): 462-8

Results: Preliminary analyses showed that MS patients had the same numeracy as the probabilistic national sample (71.6% vs. 69.2% correct answers, p=.142). In both patients and controls, higher numeracy was related to being male (p<.001), younger age (p=.037), and higher education (p<.001), see Table 1.

Table. Percentage of correctly answered items on the numeracy scale by sample (patients versus probabilistic national sample) and demographic groups

	% of Correctly Answered Items, Mean (SE)[a]	
Demographic characteristic	Patients (n = 344)	Probabilistic national sample (n = 1001)
Overall	71.6 (1.9)	69.2 (0.8)
Sex		
Male	77.5 (2.7)	75.2 (1.0)
Female	67.0 (2.6)	63.3 (1.1)
Age, y		
18 to 39	75.9 (2.2)	72.9 (1.4)
40 to 54	72.3 (2.4)	69.8 (1.2)
55 to 69	64.2 (5.7)	65.0 (1.4)
Educational level[b]		
Less than high school	57.8 (3.9)	61.7 (1.2)
High school	72.1 (3.0)	67.4 (1.3)
Some college	84.9 (2.8)	78.6 (1.5)

Notes:
[a] All data are estimated marginal means from an analysis of variance comparing numeracy scores between the samples and also including the demographic variables sex, age group, and educational level as predictors.
[b] In Germany, less than high school includes participants who finished *Hauptschule*; high school, those who finished *Realschule*; and some college, those who obtained *Abitur*.

Conclusion: MS patients had the same numeracy as a national probabilistic sample and the same demographic variables predicted numeracy in controls and patients. These results imply that MS patients understand quantitative health information as well as the general population and may be capable of understanding the benefits and risks of treatment with NAT.

Disclosure: Study sponsored by Biogen Idec GmbH.

P4146

Switching from subcutaneous interferon Beta-1a to alemtuzumab improves relapse outcomes in CARE-MS I

B. Kieseier[1], J. Lycke[2], A.N. Boyko[3], X. Montalban[4], D.H. Margolin[5], L. Kasten[6], E.J. Fox[7]

[1]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, [2]University of Gothenburg, Gothenburg, Sweden, [3]Russian Science and Research Medical University named after N. I. Pirogov and Moscow Multiple Sclerosis Center, Moscow, Russian Federation, [4]Vall d'Hebron University Hospital and Research Institute, Barcelona, Spain, [5]Genzyme, a Sanofi company, Cambridge, USA, [6]PROMETRIKA LLC, Cambridge, USA, [7]Central Texas Neurology Consultants, Round Rock, USA

Background and aims: In the 2-year, phase 3 CARE-MS I study (NCT00530348), alemtuzumab significantly reduced annualised relapse rate (ARR) in treatment-naive patients with active relapsing-remitting multiple sclerosis, compared with subcutaneous interferon beta-1a (SC IFNB-1a). This analysis investigated alemtuzumab's effects on relapse in patients who received SC IFNB-1a in CARE-MS I and switched to alemtuzumab.

Methods: In CARE-MS I, SC IFNB-1a-treated patients received 44μg 3 times/week for 2 years during the core study and 2 annual courses of alemtuzumab 12mg in the first 2 years of the extension (NCT00930553). Relapse events were assessed by raters blinded to patients' earlier treatment assignment. Evaluated endpoints included ARR, proportions relapse-free, and relapse outcomes over 2 years in all SC IFNB-1a-treated patients and in the subgroup who relapsed during the core study.

Results: The extension enrolled 144 (83%) SC IFNB-1a-treated patients from CARE-MS I. ARR decreased by 69% after switching to alemtuzumab (0.39 vs 0.12). The proportion of relapse-free patients increased after switching (79%), compared with core study SC IFNB-1a treatment (59%). In the patient subset who relapsed on SC IFNB-1a during the core study (n=60), ARR decreased after switching to alemtuzumab (0.82 vs 0.29) and 58% were relapse-free 2 years after switching. Similar results were observed in SC IFNB-1a patients who relapsed in Year 2 (n=32; ARR 1.04 vs 0.36 [47% relapse-free]).

Conclusion: Alemtuzumab treatment further decreased ARR in patients who received SC IFNB-1a in CARE-MS I. These findings highlight its superior efficacy, as shown in that randomised, head-to-head study, and demonstrate the benefits of switching to alemtuzumab.

Disclosure: Study supported by Genzyme, a Sanofi company, and Bayer Healthcare Pharmaceuticals.

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P4147

First results of a prospective cohort study in clinically isolated syndromes and early multiple sclerosis of the German Competence Network Multiple Sclerosis

A. Salmen[1], G. Antony[2], A. Ziegler[3], F. Zipp[4], B. Tackenberg[5], F. Then Bergh[6], H. Tumani[7], R. Hohlfeld[8], M. Stangel[9], C. Heesen[10], B. Wildemann[11], F. Paul[12], A. Bayas[13], B.C. Kieseier[14], F. Weber[15], R.A. Linker[16], U. Ziemann[17], U.K. Zettl[18], V. Limmroth[19], A. Chan[1], H. Wiendl[20], B. Hemmer[21], R. Gold[1]

[1]St. Josef Hospital, Bochum, Germany, [2]Philipps-University Marburg, Central Information Office (CIO), Marburg, Germany, [3]University of Lübeck, Institute of Medical Biometry and Statistics (IMBS), Lübeck, Germany, [4]University Medicine Mainz, Johannes Gutenberg University Mainz, Neurology, Mainz, Germany, [5]Philipps-Universität und Universitätsklinikum Gießen und Marburg, Klinik für Neurologie, Marburg, Germany, [6]University of Leipzig, Neurology, Leipzig, Germany, [7]University of Ulm, Neurology, Ulm, Germany, [8]Ludwig-Maximilians-Universität, Institute of Clinical Neuroimmunology, Munich, Germany, [9]Hannover Medical School, Neurology, Hanover, Germany, [10]University Hospital Hamburg-Eppendorf, Neurology, Hamburg, Germany, [11]University of Heidelberg, Neurology, Heidelberg, Germany, [12]Charité – University Medicine Berlin, NeuroCure Clinical Research Center, Berlin, Germany, [13]Klinikum Augsburg, Neurology, Augsburg, Germany, [14]Heinrich-Heine-University, Neurology, Düsseldorf, Germany, [15]Max-Planck-Institute of Psychiatry, Neurology, Munich, Germany, [16]University Hospital Erlangen, Neurology, Erlangen, Germany, [17]University Hospital, Eberhard-Karls-Universität Tübingen, Neurology, Tübingen, Germany, [18]University of Rostock, Neurology, Rostock, Germany, [19]Hospital Köln-Merheim, Neurology, Cologne, Germany, [20]University Hospital Münster, Neurology, Münster, Germany, [21]Klinikum rechts der Isar, Technische Universität München, Neurology, Munich, Germany

Background and aims: Recent epidemiological data on course and treatment of early Multiple Sclerosis (MS) in Germany is widely lacking. Other countries are hardly comparable due to differences in respective environmental and genetic factors. The German Competence Network Multiple Sclerosis (KKNMS) initiated a nationwide cohort study in clinically isolated syndrome (CIS) and early MS.

Methods: This prospective cohort study (Ruhr-University Bochum, Ethics committee reg.-no. 3714-10) recruited adult CIS and early MS patients at 22 sites in Germany. Inclusion criteria comprised newly established diagnosis of CIS with high probability of conversion to MS or relapsing-remitting MS according to current diagnostic criteria within the past two years. Therapy-naïve status for disease-modifying drugs (DMDs) was a prerequisite. Patients with progressive forms of MS or interfering neurological diseases were excluded. Clinical, MRI data and biomaterial were collected following standardized protocols and quality control with yearly visits over the first three years and every other year consecutively for another three visits.

Results: The recruitment period was Aug-2010 to Dec-2014. As of Dec-31-2014, 1208 patients were enrolled, 67 of 1208 (5.5%) had to be excluded (inclusion criteria not fulfilled, major data missing); of resulting 1141 patients, 133 (11.7%) were lost to follow-up. Analyses of baseline data and data clearing are ongoing and will be presented at the meeting.

Conclusion: This first description of a German cohort of more than 1000 newly diagnosed CIS and MS patients will allow for numerous investigations of MS disease course, usage of modern DMDs, environmental and genetic factors.

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P4148

Modeling dose-PK-lymphocytes relationship under siponimod (BAF312) treatment to infer time to immune reconstitution

C. Sarr, M. Savelieva, G. Ette, C. Petry, E. Legangneux, E. Wallstroem

Novartis Pharma AG, Basel, Switzerland

Background and aims: Siponimod (BAF312), a selective sphingosine 1-phosphate 1 and 5 receptor modulator targets multiple sclerosis (MS) by preventing circulating effector lymphocyte infiltration to central nervous system. We conducted a modeling analysis to characterize the relationship between siponimod PK exposure and lymphocyte dynamics, using clinical data from phase I and phase II studies.

Methods: Several indirect response models, including models with a feedback loop, were tested to characterize the interaction between siponimod concentrations and lymphocyte dynamics (Figure). Data from 6 phase I studies and 1 phase II study were split into: model-building dataset (5 studies) and qualification dataset (2 studies; Table 1). Covariates tested were weight, gender, MS (yes/no) and ethnicity. Simulations were performed to assess the time to lymphocyte recovery.

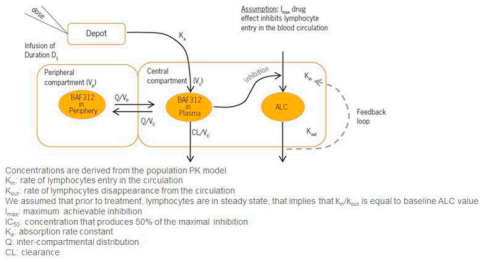

Figure: PKPD model for siponimod concentrations and absolute lymphocyte count

Study Number	Phase	Indications	Subjects included in the analysis	Treatment / Arm	Dose range (mg)
Building Dataset					
CBAF312A2101	I	HV	80	BAF312 Placebo	0.1 -75 mg
CBAF312A2105	I	HV	37	BAF312 Placebo	0.3 - 20 mg
CBAF312A2107	I	HV	37	BAF312 Placebo	0.25 - 10 mg
CBAF312A1101	I	HV	32	BAF312 Placebo	0.5 - 20 mg
CBAF312A2201	II	MS	93	BAF312 Placebo	0.25 - 10 mg
CBAF312A2201E	II	MS	93	BAF312	Doses selected during core study
Validation Dataset					
CBAF312A2110	I	HV	118	BAF312 Placebo	0.5 - 4 mg
CBAF312A2118	I	HV	92	Placebo BAF312 Moxifloxacine	2 and 10 mg

Table 1: Siponimod clinical trials pooled for analysis

Results: An indirect response model combined with an Imax model adequately characterized the relationship between siponimod PK exposure and lymphocyte dynamics. The maximal effect on lymphocyte reduction was estimated to be 84%. The IC50 on lymphocyte reduction was estimated at 4.55 ng/mL (inter-individual variability around 40%). Statistically significant covariates were: Gender on 'IC50', weight on 'Imax' and 'PK clearance', baseline on 'Kout', and disease status on 'baseline'. Table 2 summarizes median time required for lymphocyte recovery following continuous treatment with siponimod 2mg or 1mg daily.

Categories of patients and doses		Threshold of 1.0×10^9/L Median (95% Prediction Interval), days
MS patient Female	2 mg*	4 (2-9)
MS patient Male		4 (1-9)
MS patient Female	1 mg*	3 (1-7)
MS patient Male		3 (1-7)
		Threshold of 90% of baseline **Median (95% Prediction Interval), days**
MS patient Female	2 mg*	7 (4-13)
MS patient Male		7 (3-13)
MS patient Female	1 mg*	6 (3-11)
MS patient Male		5 (2-10)
		Threshold of 0.6×10^9/L# **Median (95% Prediction Interval), days**
Healthy volunteers		1 (1-3)
MS patients		2 (1-5)

*Daily treatment given during 10 days; MS, multiple sclerosis
#Many subjects did not reach this threshold at steady state

Table 2: Time in days needed to recover at different thresholds function of siponimod treatment and categories of MS patients (residual variability taken into account)

Conclusion: For the first time, the relationship between siponimod doses and their impact on lymphocytes dynamic was characterized in healthy volunteers and MS patients. Lymphocyte recovery time may be relevant for vaccinations, severe infections, therapy switch and other situations requiring reversal of pharmacodynamic effects.

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P4149

Epidemiological study to evaluate the course of disease and therapy decisions in relapsing-remitting multiple sclerosis patients with long-term first-line disease modifying treatment

S. Schmidt[1], J. Koehler[2], C. Winterstein[3], P. Schicklmaier[3], C. Wernsdoerfer[3], B. Kallmann[4]
[1]Neurologische Gemeinschaftspraxis, Bonn, Germany, [2]Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke gemeinnützige GmbH, Berg, Germany, [3]Biogen Idec GmbH, Ismaning, Germany, [4]multiple sklerose zentrum bamberg - msbz, Bamberg, Germany

Background and aims: A previous analysis has demonstrated that about 25% of RRMS patients treated with first-line DMT would have qualified for second-line treatment based on clinical and subclinical disease activity (Mäurer M. et al. Eur J Neurol 2011). It is unknown whether this situation has changed in the context of new therapeutic options and risk stratification tools.

Methods: This non-interventional multicenter study retrospectively evaluated the clinical course of disease, MRI, and QoL of 4215 RRMS patients treated with first line DMTs for ≥ 24 months from October 2010-June 2014. The assessment of the clinical disease course by the treating neurologists and the resulting treatment decisions were analyzed.

Results: Baseline demographics: mean age 44.8 years, 73.1% females, median disease duration 9.6 years, mean EDSS 2.3. In 1594 patients, EDSS, MRI, relapse rate, judgment of disease course by the treating neurologists as well as treatment decisions were available. Although evidence of clinical and/or MRI activity was detectable in 50.8% of these patients, 64.8% were rated as "stable", 2.3% even as "improved" and only 31.9% as "worsened". Treatment optimization was considered for only 24.7% of these patients.

Conclusion: The treating physicians considered the majority of patients as „stable" despite evidence of clinical and/or subclinical disease activity. Therefore only a minority was considered suitable for treatment optimization. This study underlines the importance to understand and develop clinical and subclinical measures of disease activity in MS in order to improve the monitoring of treatment responses to DMTs and to optimize treatment decisions.

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P4150

Exosomal RNA sequences as biomarkers of MS

I. Selmaj, K. Selmaj, M. Mariasiewicz, M. Mycko
Medical University of Lodz, Department of Neurology, Laboratory of Neuroimmunology, Lodz, Poland

Background and aims: Exosomes are a membrane vesicles released from the endocytic compartment of live cells that play an important role in cell-to-cell communication. The major contents of the exosomes are short RNAs that can interfere with the function of the acceptor cells.

Methods: To analyze the role of exosomes in the relapsing remitting multiple sclerosis (MS) we have isolated exosomes and exosomal RNA from serum and urine of the MS patients and control subjects. Subsequently we have generated exosomal RNA libraries and process them for the next generation sequencing analysis.

Results: We have found that both serum and urine exosomes are a reach source of the shortRNA (<300 nt) in MS patients. RNA-seq yielded an average of 4019 different annotated sequences in serum exosomes of MS patients during relapse, whereas 2877 sequences in the MS during remission and 3075 sequences in control subjects. The urine exosomal RNA analysis have demonstrated presence of 4480 different annotated RNA sequences in material from MS patients during relapse whereas only 1093 different sequences in material from controls. All the sequences have been grouped into 14 different RNA categories: CDBox, HAcaBox, RefSeq_antisense, lincRNA, lincRNA_antisense, miRNA, other_ncRNA, other_ncRNA_antisense, rRNA, piRNA, rfam, scaRNA, tRNA and tRNA_like. RefSeq_antisense represented the largest fraction of frequences derived from MS patients serum or urine exosomes (22 to 28% of sequences).

Conclusion: Our data highlight a potential difference in serum and urine exosomes RNA in MS patients related to the clinical status of the patients that could lead to a discovery of new biomarkers of MS.

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P4151

Abstract cancelled

P4152

Understanding the characteristics of secondary progressive multiple sclerosis to facilitate early identification

D. Simsek[1], E. Verdun[1], R. Lahoz[1], J. Pike[2], E. Jones[2]
[1]Novartis Pharma AG, Basel, Switzerland, [2]Adelphi Real World, Macclesfield, United Kingdom

Background and aims: The transition from Relapsing-remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis (SPMS) may be lengthy and there is no single standard definition of SPMS broadly applied in clinical practice. We assessed the differences between late-RRMS and early-SPMS patients on sociodemographics, daily activities and clinical characteristics including symptoms and MRI parameters.

Methods: Data were drawn from the Adelphi Multiple Sclerosis Disease Specific Program, a cross-sectional study of 250 neurologists and 3294 patients in the US. 343 patients diagnosed with MS at least 4 years and EDSS≥3 were analyzed; 261 were defined as late-RRMS (Physician designation of RRMS and EDSS<6) and 82 as early-SPMS (Physician designation of SPMS ≤3 years). Fisher's Exact test and Mann-Whitney test for categorical and continuous outcomes respectively, were used to determine unadjusted differences in the two groups. Further multivariate analyses are being performed.

Results: In unadjusted analyses, early-SPMS patients were found to be older, less likely to be employed, required more help with activities of daily living, suffered from more frequent motor and urinary symptoms, and had more T2 lesions (Table). A near-significant difference was observed in the frequency of sensory symptoms.

	Late-RRMS	Early-SPMS	P-value
Mean Age - years (n)	45.8 (261)	50.0 (82)	0.001
Employed n (%)	108 (41.38)	12 (14.63)	<0.001
Require help for ADL n (%)	148 (57.59)	71 (87.65)	<0.001
Motor symptoms n (%)	219 (83.91)	77 (93.90)	0.026
Urinary symptoms n (%)	102 (39.08)	47 (57.32)	0.005
Mean No. of T2 lesions (n)	8.0 (192)	12.7 (67)	0.005
Sensory symptoms n (%)	150 (57.47)	56 (68.29)	0.093

ADL, activities of daily living; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table: Sociodemographics and clinical characteristics of Late-RRMS and Early-SPMS patients (Unadjusted analysis)

Conclusion: These analyses highlight significant differences between RRMS and SPMS populations. These variables could be useful parameters for physicians to consider when assessing the transition from RRMS to SPMS. Accurate early identification of SPMS patients and use of the most appropriate treatments may result in better long-term outcomes for this population.

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P4153

Sympathetic autonomic system is differentially altered in progressive and relapsing multiple sclerosis

V. Studer, C. Rocchi, C. Motta, B. Lauretti, G.A. Marfia, D. Centonze, S. Rossi
Tor Vergata University, Rome, Italy

Background and aims: Sympathovagal imbalance has been associated to poor prognosis in several chronic diseases, but conflicting evidence have been reported about autonomic nervous system (ANS) dysfunction in multiple sclerosis (MS). We aimed to assess ANS dysfunction in MS and its correlation with progressive and worsening disability.

Methods: Heart rate variability (HRV) was analyzed in 120 MS patients and 60 healthy controls (HC) during supine rest and head up tilt test (HUTT); the normalized unit of LF and HF power (LFnu; HFnu) were considered to assess sympathetic and vagal components, respectively. Correlation analyses with clinical and radiological markers of disease activity and progression were performed.

Results: Sympathetic dysfunction was closely related to the progression of disability in MS: progressive MS patients showed altered HRV respect to HC and relapsing remitting patients (RRMS), with higher LFnu at rest and a lack of the expected LFnu increase during HUTT. Among RRMS subjects disease activity, even subclinical, was associated to lower LFnu at rest, and to an enhanced sympathetic reactivity during HUTT, whereas stable RRMS did not differ from HC. Higher LFnu increase during HUTT was observed in active patients without clinical expression of brain inflammation, while less sympathetic reactivity and higher LFnu at rest were associated with incomplete recovery from relapse. Sympathovagal balance was not influenced by the presence of infratentorial demyelinating lesions.

Conclusion: The sympathetic system is overactive and exhausted in progressive disease, ineffective in worsening MS. ANS dysfunctions appear intimately linked with both the proinflammatory environment and the compensatory plastic processes in MS.

Disclosure: Nothing to disclose

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P4156

Multiple acyl-CoA dehydrogenase deficiency in an adult: a case report

C. Duque[1], A. Gouveia[1], J. Tomás[1], E. Rodrigues[2], M.D.C.R.R.M. Macário[1]
[1]Coimbra, Portugal, [2]Centro Hospitalar do Funchal, Neurology Department, Funchal, Portugal

Background and aims: Multiple acyl-CoA dehydrogenase deficiency (MADD) is caused by defects in the pathway for transferring electrons from the first step in oxidation to the electron transport system. MADD is a clinically heterogeneous disorder of fatty acid and amino acid oxidation caused by mutations in the ETFA, ETFB and ETFDH genes.

Methods: A 32-year-old man was referred to the neurology department for muscular pains with weakness exacerbated after exertion since the age of 6. Laboratory assessment revealed an increased level of creatine kinase (529 mg/dL), ECG showed frequent ventricular extrasystoles, echocardiogram was normal and cardiac stress test was interrupted at 10 minutes due to maximal fatigue with diminished functional capacity. Acylcarnitine profile analysis showed low C2 and free carnitine and increased carnitine C5-C14, which was diagnostic for MADD. Genetic analysis identified a pathogenic mutation in the ETFH gene (p.P534L). Exon sequencing was performed and identified other pathogenic alterations, not previously described in the literature, in ETFA and ETFB genes (p.T171I and p.T245M, respectively). After family genetic studies, the mother of the patient was identified as a carrier of the pathogenic mutation and, by exon sequencing, had also the new ETFB variant.

Results: We report a patient with MADD diagnosed in adulthood, with a new genetic variant identified by exon sequencing, as combined polygenic heterozygosity.

Conclusion: Clinical presentation of MADD may range from a severe neonatal presentation to a mild childhood/adult disease with episodic metabolic decompensation, muscle weakness and respiratory failure, posing diagnostic challenge.

Disclosure: Nothing to disclose

P4157

Novel POLG1 mutations and variable clinical phenotypes in 13 italian patients

P. Da Pozzo[1], E. Cardaioli[1], A. Rubegni[2], G.N. Gallus[1], A. Malandrini[1], A. Rufa[1], C. Battisti[1], M.A. Carluccio[1], R. Rocchi[1], F. Giannini[1], A. Bianchi[3], M. Mancuso[4], G. Siciliano[4], M.T. Dotti[1], A. Federico[1]
[1]University of Siena, Department of Medical, Surgical and Neurological Sciences, Sienna, Italy, [2]IRCCS Stella Maris, Pisa, Italy, [3]Hospital, Department of Neuroscience, Arezzo, Italy, [4]University of Pisa , Department of Neuroscience, Neurological Clinic, Pisa, Italy

Background: The POLG gene encodes the catalytic subunit of DNA polymerase gamma, essential for mitochondrial DNA (mtDNA) replication and repair. Mutations in POLG have been linked to a spectrum of clinical phenotypes, resulting in autosomal recessive or dominant mitochondrial diseases. These mutations have been associated with heterogeneous phenotypes, presenting with varying severity and at different ages of onset, ranging from the neonatal period to late adult life.

Objective: To determine the spectrum of POLG mutations in a cohort of patients with clinical presentations suggestive of POLG deficiency, to evaluate the pathogenicity of novel mutations and to establish genotype-phenotype correlations.

Methods: We screened 13 patients for POLG mutations. All patients underwent a complete neurological examination, in most of cases muscle biopsy was performed.

Results: We detected 14 different mutations in 13 unrelated Italian patients. Three mutations were novel, 2 mapped in the pol domain (p.Thr989dup, p.Ala847Thr) and 1 in the linker region (p.His613Tyr) of the enzyme. We also report new cases carrying controversial mutations previously described as incompletely penetrant or a variant of unknown significance.

Discussion and Conclusions: Our results confirm the clinical heterogeneity of POLG-related diseases, underlining some peculiar clinical features, such as early onset myopathy with severe cerebellar atrophy, PEO associated with corneal edema, and epilepsy, severe neuropathy with achalasia. The addition of three new substitutions, including the second report of an in-frame duplication, to the growing list of defects increases the value of POLG genetic diagnosis in a range of neurological presentations.

Disclosure: Nothing to disclose

P4158

Clinical and genetic heterogeneity in six patients with limb-girdle muscular dystrophy type 2A

G.N. Gallus[1], A. Rubegni[2], A. Malandrini[1], S. Aguti[1], F. Sicurelli[1], C. Battisti[1], A. Rufa[3], G. Berti[1], E. Cardaioli[1], P. Da Pozzo[1], A. Federico[1]

[1]University of Siena, Department of Medical, Surgical and Neurological Sciences, Sienna, Italy, [2]2IRCCS Fondazione Stella Maris, Pisa, Italy, [3]University of Siena, Neurology and Neurometabolic Diseases Unit, Department of Medicine, Surgery and Neuroscience, Sienna, Italy

Background and aims: Limb-girdle muscular dystrophies type 2A (LGMD2A) is the most frequent form of recessive LGMD and it is caused by mutation in the CAPN3 gene. LGMD2A is characterized by progressive weakness of proximal muscles with onset ranging from two to 40 years.
To describe clinical, histological and molecular findings of six patients, belonging to four families, carrying CAPN3 mutations.

Methods: Each patient underwent a complete neurological examination and a muscle biopsy. In all cases histological, immunohistochemical and genetic studies were performed.

Results: All patients presented limb-girdle muscle weakness but were still ambulant at the last observation. Muscle biopsy showed severe dystrophic features in two and moderate myopathic changes in four cases. In the first patient we found the c.1401_1403delGGA and c.2257G>A (in cis) and the c.967G>T variant in CAPN3. In another family, two siblings harbored c.755T>G and c.1746-20C>G mutations whereas a third sib, carried only the heterozygous c.755T>G. We detected only the heterozygous c.526G>A in the proband of the third family but we observed a strongly decreased CAPN3 mRNA. Finally the sixth patient carried the heterozygous missense mutation c.2458T>C. The latter mutations were novel.

Conclusion: These findings further expands the spectrum of CAPN3 mutations. We suggest that molecular analysis based on CAPN3 gene sequencing could not be considered conclusive. In particular, in cases of heterozygosity the research of the second mutation, should continue with the analysis of the transcript and possible gene rearrangements. Finally, this study confirms the genetic and phenotypic variability in patients with LGMD2A.

Disclosure: Nothing to disclose

P4159

An adult patient with rare recessive lipodystrophy: autoinflammation, lipodystrophy, and dermatosis syndrome

A. Gouveia[1], J. Cardoso[2], C. Duque[1], J. Tomás[1], M. Gama[3], I. Alonso[3], J. Silva[3], L. Ribeiro[4], M.C. Macário[1]

[1]Coimbra University and Hospital Centre, Coimbra, Portugal, Neurology, Coimbra, Portugal, [2]Coimbra University and Hospital Centre, Coimbra, Portugal, Dermatology, Coimbra, Portugal, [3]Institute for Molecular and Cell Biology, Porto, Portugal, Porto, Portugal, [4]Coimbra University and Hospital Centre, Coimbra, Portugal, Hematology, Coimbra, Portugal

Background and aims: Autoinflammation, Lipodystrophy, and Dermatosis Syndrome (ALDS) is a rare genetic lipodystrophy, recently described, caused by homozygous mutation in the PSMB8 gene on chromosome 6p21. The few patients reported to date present panniculitis-induced childhood onset lipodystrophy, muscle atrophy, joint contractures, microcytic anemia, hepatosplenomegaly and basal ganglia calcification.

Case Report: We report the detailed phenotype of a 29-year-old Portuguese male.

Results: Our patient was born to consanguineous parents in third degree. In the first month of life, he presented recurrent erythematous skin lesions, hepatosplenomegaly and cortico-responsive microcytic anemia. During childhood, he developed progressive and severe lypodistrophy, muscle atrophy and joint contractures. In the adulthood, he manifests corneal lesions, responsive to ophthalmic cyclosporine. There is no evidence of cognitive dysfunction, however, the patient is highly dependent due to severe motor impairments. The patient underwent a thorough investigation including muscle biopsy showing necrosis, atrophy and Sudan+ cells, and pallidal calcifications in the brain MRI. Genetic testing confirmed the presence of homozygous mutation in the PSMB8 gene (c.224C> T).

Conclusion: We present a rare autosomal recessive lipodystrophy with neurologic involvement. To our knowledge, compared to the patients reported in literature, our patient has the earliest onset and is the only one with corneal lesions. The remaining phenotype is similar. The cortico-responsive anemia and the corneal lesions responsive to cyclosporine support the hypothesis of an immune dysregulation physiopathology.

Disclosure: Nothing to disclose

P4160

Vanishing white matter disease – a single centre cohort

A. Gouveia[1], J. Tomás[1], C. Duque[1], O. Galego[2], M. Arenga[1], F. Sobral[1], I. Alonso[3], J. Silva[3], M. Gama[3], F. Magalhães[1], M.C. Macário[1]

[1]Coimbra University and Hospital Centre, Neurology, Coimbra, Portugal, [2]Coimbra University and Hospital Centre, Neurorradiology, Coimbra, Portugal, [3]Institute for Molecular and Cell Biology, Porto, Portugal, Porto, Portugal

Background and aims: Vanishing white matter disease (VWMD) is a genetic leucoencephalopathy, with great phenotypic variation. MRI is frequently diagnostic and indicative of vanishing of the cerebral white matter (WM).

Methods: Retrospective review of all patients followed in our neurometabolic outpatient clinic since 2003 with the diagnosis of VHMD.

Results: We identified 7 patients. 5 were female and two were sisters. The age of neurological symptoms onset was between 17 and 46 years. 4 patients had a progressive course with spastic tetraparesis or paraparesis, urinary incontinence, dysphasia and/or neuropsychiatric symptoms (aggressiveness, disinhibition, attention deficit or memory difficulties). 3 patients exhibit acute or hyperacute presentation with seizures or subacute neurological neurological deficits followed by rapidly progressive deterioration, becoming wheel-chair bound and totally dependent in few days. Infertility was present in 2 women and hypogonadism in 1 man. All the patients fulfilled MRI VWMD criteria, namely supratentorial WM involvement with signal intensity close to that of CSF on FLAIR imagens, cystic degeneration, preservation of U fibers, corpus calosum atrophy and cerebellar WM involvement. All had homozygous mutation in EIF2B5 gene, except for one patient, who had compound heterozygous mutation in the same gene.

Conclusion: In our institution, VWMD is the most frequent leukodystrophy found in adulthood. Therefore, we think that in age group, VWMD should be excluded amongst the other currently known leukodystrophies, including that related to inborn errors of metabolism.

Disclosure: Nothing to disclose

P4161

De novo mutations in SPG3A: a challenge in differential diagnosis and genetic counselling

S. Haggiag[1], L. Leonardi[2], C. Marcotulli[3], L. Lispi[1], F. Pierelli[2], A. Tessa[4], M. Sessa[5], S. Orcesi[6], C. Cereda[6], F.M. Santorelli[4], C. Casali[2]

[1]San Camillo-Forlanini Hospital, Neurology, Rome, Italy, [2]"Sapienza" University Polo Pontino, Latina, Italy, [3]"La Sapienza" University of Rome, SBMC, Rome, Italy, [4]IRCCS Stella Maris, Developmental Neuroscience, Pisa, Italy, [5]IRCCS - Fondazione Centro S.Raffaele del Monte Tabor, Milan, Italy, [6]IRCCS C. Mondino , Pavia, Italy

Background and aims: Early-onset HSP SPG3A (OMIM 182600) is caused by mutations in the gene encoding the large oligomeric GTPase atlastin-1 protein. Mutations in SPG3A (also known as atlastin GTPase 1 [ATL1]) cause both pure and uncomplicated phenotypes with early onset and slow progression. SPG3A/ATL1 mutations represent the most frequent cause of early onset HSP. De novo occurrence of SPG3A/ATL1 mutations in isolated cases poses diagnostic challenge and patients are easily misdiagnosed with a non inheritable, non trasmissable form of spastic paraplegia.

Methods: Herein, we describe three patients with infantile onset HSP harbouring de novo mutations, including a new variant, in SPG3A/ATL1.

Results: Patient-1 is 50 y with clinically pure HSP, misdiagnosed in childhood as cerebral palsy. Genetic counseling in his early adulthood excluded hereditary diseases. Subsequently he fathered a similarly affected daughter. Both subjects had a heterozygous c.859C>T (p.R239C) mutation in SPG3A gene. Patient-2 is 3 y, with a pure form of HSP, associated with (c.1308 T>A/p.N436K) mutation in SPG3A, which was absent in either his healthy parents. Patient-3 is 15 y with a moderate form of HSP associated with axonal neuropathy since his childhood. A c.1040T>C (p.M347T) heterozygous mutation in SPG3A was identified in the patient but not in his healthy parents.

Conclusion: Infantile onset HSP represents a challenging differential diagnosis, particularly when there is no family history. Patients are often diagnosed as „infantile cerebral palsy", no genetic counseling is offered and the diagnosis can be significantly delayed.

Disclosure: Nothing to disclose

P4162

Novel GBE1 gene mutation in Japanese family with adult polyglucosan body disease

Y. Harigaya[1], T. Matsukawa[2], Y. Fujita[3], A. Sekine[1], M. Imamura[4], K. Mizushima[1], Y. Ikeda[3], S. Tsuji[2]
[1]Maebashi Red Cross Hospital, Neurology Service, Maebashi, Japan, [2]Tokyo University Graduate School of Medicine, Department of Neurology, Tokyo, Japan, [3]Gunma University Graduate School of Medicine, Department of Neurology, Maebashi, Japan, [4]Haramachi Red Cross Hospital, Department of Internal Medicine, Haramachi, Japan

Background and aims: Adult polyglucosan body disease (APBD) is an autosomal recessive leukoencephalopathy characterized by progressive neurogenic bladder, gait disturbance and peripheral neuropathy due to polyglucosan bodies deposition in the central and peripheral nervous systems. Eleven disease-causing mutations in GBE1 gene have been described.

We performed exome sequencing and identified a GBE1 homozygous novel mutation in Japanese brothers with APBD.

Methods: Two brothers (case 1, 2; 72, 66 years old, respectively) with consanguineous parents were admitted for gait disturbance. Both showed leg muscle weakness with atrophy, generalized hyporeflexia, and urinary incontinentia. Extensor plantar reflexes and leg myoclonus were observed in case 1, and opthalmoplegia, bulbar palsy and distal lower extremity sensory disturbance in case 2.

Fluid attenuated inversion recovery magnetic resonance imaging demonstrated hyperintense white matter abnormalities predominantly in the periventricular regions, posterior limb of the internal capsule, and pyramidal tracts of the pons and medulla, and medulla and spine atrophy.

Electromyography and nerve conduction studies revealed axonal sensory-motor neuropathy predominantly in the lower limbs. Muscle biopsies showed small group atrophy indicating denervation.

Results: Exome sequencing demonstrated a G to A transition at position 929 in a homozygous state, with replacement of tyrosine with cysteine at codon 310 (Tyr310 Cys) of GBE1 gene, which was also found in a heterozygous state in their asymptomatic younger sister.

APBD was confirmed by deposition of polyglucosan bodies in sural nerve biopsy from case 1.

Conclusion: We report a GBE1 homozygous novel mutation causing APBD. For the differential diagnosis of leukoencephalopathy, APBD should be considered.

Disclosure: Nothing to disclose

P4163

A distinct type of 3-methylglutaconic aciduria due to a novel mutation in the Translocase of Inner Mitochondrial Membrane 50 (TIMM50) gene

F. Serajee, A. Huq
Wayne State University, Pediatrics and Neurology, Detroit, USA

Background and aims: 3-methylglutaconic aciduria is a heterogeneous group of disorders and includes leucine metabolism abnormality and several mitochondrial protein import disorders. We report a homozygous mutation in mitochondrial TIMM50 gene in a family with 3 affected siblings with a distinctive type of 3-methylglutaconic aciduria. Currently TIMM50 gene mutation is not known to cause any Mendelian disorder in human.

Methods: We investigated a patient of South Asian ancestry with intractable epilepsy, microcephaly, developmental delay and spastic quadriplegia. Parents were consanguineous and two earlier-born sisters of the patient with a similar phenotype had died unexpectedly after an infection. All three siblings excreted large amount of 3-methyl glutaconic acid in urine. We performed full exome sequencing using genomic DNA isolated from one surviving patient, two healthy siblings and both parents.

Results: Exome sequencing identified a homozygous c.1114G>A (p.G372S) mutation in the gene TIMM50 which encodes Tim50, an important component of mitochondrial import machinery. The G372 amino acid position is completely conserved evolutionally. The p.G372S alteration is predicted to be damaging and deleterious by PolyPhen and SIFT and is located in the conserved C-terminal domain of the Tim50 protein that interacts with Tim23 protein in the intermembrane space and regulates import of presequence-containing polypeptides into mitochondria. Both parents were heterozygous. The patient's healthy sister was homozygous normal and her healthy brother was heterozygous. No other candidate alteration in exome explains the patient's phenotype.

Conclusion: TIMM50 gene mutation results in a novel mitochondrial membrane associated disorder with a distinct phenotype and 3-methyl glutaconic aciduria

Disclosure: Nothing to disclose

Neuroimaging 3

P4164

Multimodal characterization of default mode network structure and metabolism in patients with disorders of consciousness using diffusion weighted-MRI and 18F-FDG-PET.

J. Annen[1], L. Heine[1], E. Ziegler[2], J. Stender[3], M.A. Bahri[2], S. Wannes[1], M.-A. Bruno[1], A. Thibaut[1], C. Bernard[4], G. Antonopoulos[2], C. Di Perri[2], C. Martial[1], E. Amico[2], A. Demertzi[2], E. Salmon[2], P. Maquet[1], J.-F.L. Tshibanda[4], R. Hustinx[4], S. Laureys[1]

[1]University of Liège, Cyclotron Research Centre, University Hospital of Liège, Liege, Belgium, [2]University of Liège, Cyclotron Research Centre, Liege, Belgium, [3]University of Copenhagen, Department of neuroscience and pharmacology, Copenhagen, Denmark, [4]University Hospital of Liège, Liege, Belgium

Background and aims: The precise relationship between white matter structural connectivity and metabolic function is not yet completely understood. Patients with disorders of consciousness offer a unique population to study this. Here we examined whether the relationship between structural connectivity and metabolic function is altered in these patients.

Methods: We studied 27 patients and 14 healthy subjects using two neuroimaging modalities: diffusion-weighted MRI and 18F-FDG-PET imaging (Figure 1). We analyzed the default mode network (thalamus, frontal cortex, precuneus, inferior parietal cortex) white matter integrity by constructing white matter brain networks using fiber tractography, and calculating the fractional anisotropy within each connection between the four regions. Additionally, standardized uptake values (SUV) were calculated for each region. Structural and functional markers from the best functioning hemisphere of each subject (defined by total SUV from all four regions) were examined for correlations.

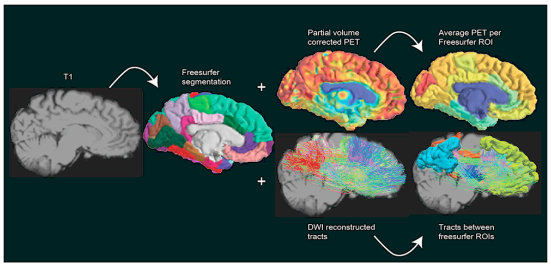


Figure 1

Results: Healthy controls showed a positive linear correlation between structural connectivity (fractional anisotropy) in the mesio-frontal to precuneus cingulate connection and brain metabolism (SUV) in the frontal cortex and precuneus, while the correlation was absent in brain injured patients (controls r=0.61 & 0.53 respectively, patients r=0.00 & -0.04 respectively, Fisher's z-score = -1.95 & -1.77, $p<0.05$, Figure 2).

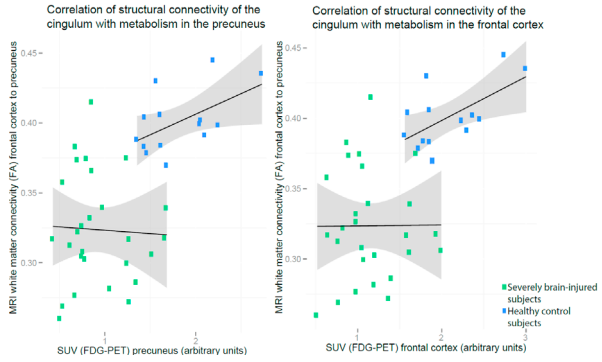


Figure 2

Conclusion: These results imply that the coupling between structure (diffusion weighted-MRI) and brain metabolism (FDG-PET) existing in healthy volunteers is seemingly absent in severely brain injured patients.

Disclosure: Nothing to disclose

P4165

Diagnostic accuracy of cerebral metabolic imaging in disorders of consciousness

G. Antonopoulos[1], S. Wannez[2], A. Thibaut[1], A. Luxen[1], M.A. Bahri[1], R. Hustinx[3], C. Bernard[3], M.-A. Bruno[4], C. Chatelle[5], C. Phillips[1], P. Maquet[6], S. Laureys[4]
[1]University of Liège, Cyclotron Research Centre, Liege, Belgium, [2]ULg, Cyclotron Research Centre, Liege, Belgium, [3]University Hospital of Liège, Liege, Belgium, [4]Liege, Belgium, [5]Harvard Medical School, Rehabilitation Hospital, Liege, Belgium, [6]University of Liège, Cyclotron Research Centre, University Hospital of Liège, Liege, Belgium

Background and aims: The high rate of misdiagnosis (1) reflects the difficulty of correctly diagnosing different states of consciousness like minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome (VS/UWS). Currently, there is no method that can give an objective measure of consciousness and therefore multiple clinical examinations are required for the evaluation of a patient's consciousness state. We here aim to develop an evaluation method by teaching a machine to detect the state of consciousness using fluorodeoxyglucose PET (18F-FDG-PET) scans.

Methods: PET scans of 136 patients (table 1), were acquired in the University Hospital of Liege. Each patients' state of consciousness was evaluated with repeated assessments of Coma Recovery Scale. Data were preprocessed and analyzed by means of statistical parametric mapping (SPM12) (figure 1). For the intensity normalization purposes, skin metabolic activity was used. For classification and statistical inference we used the Pronto toolbox.

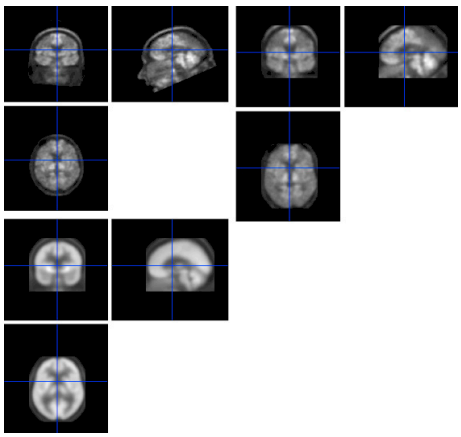


Figure 1: Top row represents PET-scans before (left) and after (right) normalization. Bottom row depicts the study specific template used for the normalization.

Results: The total classification accuracy was 78% by using a cross validation scheme. 83 out of 94 MCS patients were correctly classified. Since the classifier we used assigns one value to each voxel, this can be displayed as weight map (figure 2). This weight map depicts the lilkelihood for each voxel to belong to the MCS or the VS/UWS class.

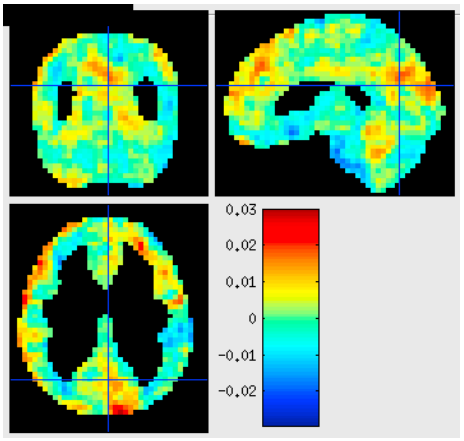


Figure 2: Voxels' weights extracted from the training process of the classifier

Conclusion: Medial and lateral frontoparietal cortices and brain stem appear to play a key role in consciousness state, as shown by the weights assigned by the classifier to the voxels. Besides the absolute cortical metabolic activity (2), glucose consumption in different brain regions can affect the state of consciousness.

Disclosure: Nothing to disclose

P4166

Usefulness of FDG-PET in the differential diagnosis of parkinsonian syndromes on an individual basis.

R. Ceravolo[1], D. Frosini[1], A. Accorroni[1], A. Giorgetti[2], G. Puccini[3], E. Filidei[2], D. Volterrani[3], U. Bonuccelli[1]
[1]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [2]Fondazione Monasterio, Nuclear Medicine, Pisa, Italy, [3]University of Pisa, Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy

Background and aims: Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) can identify characteristic patterns of regional glucose metabolism in Parkinson's disease (PD) and atypical parkinsonisms, however most previous studies were conducted in late disease stages and based on a group-comparison approach. Aim of this study is to evaluate the diagnostic accuracy of FDG-PET in parkinsonisms on an individual basis.

Methods: 101 patients with parkinsonisms underwent FDG-PET at baseline and were then followed-up for 5 years, in order to maximize the diagnostic confidence. The FDG-PET were then retrospectively evaluated by two blinded examiners after images post-processing by the software Pneuro, which allows to obtain for each patient a map showing the regions with metabolic changes ($p<0.01$) respect to a database of healthy controls

Results: The diagnosis at follow-up were: 17 PD (mean age 65), 23 Multiple System Atrophy (MSA) (age 72), 30 Progressive Supranuclear Palsy (PSP) (age 74), 16 Cortico-Basal Degeneration (CBD) (age 72), 15 Lewy Body Dementia (LBD) (age 75). The sensitivity, specificity, positive and negative predictive value for atypical parkinsonisms with respect to PD for the two readers and both the diagnostic accuracy and concordance with clinical diagnosis for each disease on individual basis are reported in table 1. The inter-rater agreement was between 0.60 and 0.86 according to Cohen's kappa coefficient.

Table 1. Diagnostic concordance on individual basis

	Atypical Parkinsonism	PD	MSA	PSP	CBD	LBD
Reader 1						
Sensitivity	94%	88%	83%	70%	75%	87%
Specificity	88%	94%	97%	92%	96%	94%
PPV	98%	75%	90%	78%	80%	72%
NPV	75%	98%	95%	88%	95%	98%
Reader 2						
Sensitivity	89%	75%	78%	70%	75%	75%
Specificity	75%	89%	95%	97%	95%	95%
PPV	95%	57%	82%	91%	75%	69%
NPV	57%	95%	93%	88%	95%	96%

FDG-PET diagnostic accuracy on individual basis in parkinsonisms

Conclusion: Our data demonstrate the usefulness of a computer-supported FDG-PET analysis to help the clinicians in early distinction between PD, PSP, MSA, CBD and LBD from each other on a single case basis.

Disclosure: Nothing to disclose

P4167

Pattern of regional cortical thickness in patients with Parkinson's disease and impulse control disorders

R. De Micco[1], G. Santangelo[2], C. Vitale[3], A. Tessitore[1], M. Amboni[4], D. Corbo[3], A. Giordano[1], P. Barone[5], G. Tedeschi[1]
[1]Second University of Naples, Department of Neurology, Naples, Italy, [2]Second University of Naples, Department of Psychology, Caserta, Italy, [3]Institute for Diagnosis and Care "Hermitage Capodimonte", Naples, Italy, [4]Institute for Diagnosis and Care "Hermitage Capodimonte", Naples, Italy, [5]University of Salerno, Department of Medicine and Surgery, Salerno, Italy

Background and aims: To investigate the pattern of gray matter (GM) atrophy and cortical thickness (CTh) in patients with Parkinson's disease (PD) with and without impulse control disorders (ICD).

Methods: 15 patients with PD with ICD (ICD+), 15 patients with PD without ICD (ICD-) and 24 age and sex-matched healthy controls (HCs) were enrolled in the study. Patients were screened for ICDs by the Minnesota Impulsive Disorders Interview (MIDI). Whole brain structural imaging was performed on a 3T GE MR scanner. Surface-based investigation of CTh was carried out by using Freesurfer Software. We also used voxel-based morphometry to investigate the pattern of GM atrophy. We considered cortical areas with the p value less than 0.05 corrected for multiple comparisons as statistically significant.

Results: The voxel-wise analysis of the regional differences in CTh revealed a specific abnormal pattern involving the limbic system in the comparisons between: a) ICD- and ICD+ patients and b) ICD+ patients and HCs. In particular, ICD+ patients showed a statistically significant ($p<0.05$) cortical thickening when compared to both ICD-patients and HCs in the anterior cingulate (ACC) and orbitofrontal (OFC) cortices. Moreover, cortical thickening in these areas is correlated ($p<0.05$) to MIDI score. VBM data did not reveal any statistically significant differences in GM.

Conclusion: Our results demonstrated that ICD+ patients have a stronger pattern of CTh in limbic regions compared with ICD-. Thus, aberrant anatomical and cytoarchitectural features in OFC and ACC, involved in reward-related decision making, may play a role in the lack of inhibition of compulsive behaviors.

Disclosure: Nothing to disclose

P4168

The neural correlates of the emergence from disorders of consciousness: a multi-modal neuroimaging study

C. Di Perri[1], M.A. Bahri[1], E. Amico[1], A. Thibaut[1], M.-A. Bruno[1], A. Demertzi[1], L. Heine[2], S. Wannez[3], F. Gómez[1], J. Annen[4], P. Guldenmund[5], P. Maquet[2], R. Hustinx[6], J.-F.L. Tshibanda[6], A. Soddu[5], S. Laureys[7]

[1]University of Liège, Cyclotron Research Centre, Liège, Belgium, [2]University of Liège, Cyclotron Research Centre, University Hospital of Liège, [3]ULg, Cyclotron Research Centre, [4]ULg, [5]Coma Science Group, [6]University Hospital of Liège, [7]Liège, Belgium

Background and aims: Between severe disorders of consciousness (DOC, i.e. vegetative state/unresponsive wakefulness syndrome - VS/UWS - and minimally conscious state - MCS -) and normal consciousness (healthy controls) there is a widely under-investigated transition zone represented by those patients who regained capacity for functional communication and/or object use, also called emerging from minimally conscious state (EMCS).

We hereby aim to study the role of brain metabolism, grey matter volume, positive and negative resting state functional connectivity (i.e., neuronal correlation and anticorrelation) in the emergence from DOC.

Methods: We acquired FDG-PET, structural MRI and resting-state functional MRI in 58 severely brain injured patients (23 VS/UWS, 21 MCS, 14 EMCS) and 37 age-matched healthy controls. Voxel-based neuroimaging analyses were performed using SPM8. We used a seed-based approach to investigate positive connectivity within the default mode network (DMN) and negative connectivity between default mode network (DMN) and task positive network (TPN).

Results: Brain metabolism in DMN and TPN was correlated with the levels of consciousness.

Grey matter volume did not show a linear correlation with the levels of consciousness.

Positive connectivity within DMN could not discriminate EMCS from DOC (Fig.1A). Negative connectivity between DMN and TPN disentangled EMCS from DOC (Fig.1B-C). Brain metabolism was correlated with both positive and negative connectivity (Fig. 2).

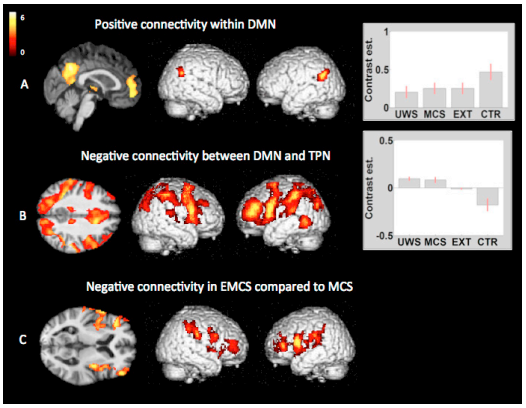


Fig 1. VS/UWS vegetative state/unresponsive wakefulness; MCS minimally conscious state; EXT: emergence from minimally conscious state: CTR healthy controls; DMN default mode network; TPN task positive network. Results are p<0.05 FDR corrected

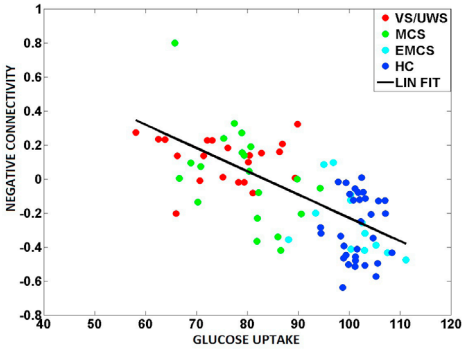


Fig 2. VS/UWS vegetative state unresponsive wakefulness syndrome: MCS minimally conscious state; EMCS emergence from minimally conscious state; HC healthy controls.

Conclusion: Negative functional connectivity between DMN and TPN is correlated to brain metabolism and seems critical for the emergence from DOC.

Disclosure: Nothing to disclose

P4169

Cerebellar function in motor timing

P. Filip[1], R. Mareček[1], M. Bares[2]
[1]*St. Anne University Hospital, Brno, Czech Republic,* [2]*Brno, Czech Republic*

Background and aims: The cerebellum has been associated exclusively with motor functions for a long time. However, its activation has been increasingly shown in a wide spectrum of different processes extending far beyond the typical cerebellar domain, including attention, motivation control, associative learning, and time assessment. The precise role of individual cerebellar lobuli in these functions has lately been of great interest. In our study, we have focused on time assessment in specific motor timing task, previously shown to be closely associated with cerebellum.
Methods: Functional magnetic resonance imaging has been performed in 30 healthy individuals during an interception of a moving target. The subjects were asked to press a button in a precise time frame to hit the moving target. This action required complex time estimation and anticipation, as the subject had to react in advance according to the speed of the target to intercept it successfully. In a simplified control task, there was no need for reacting in advance, as the subjects were asked to press the button when the moving target reached a specific area marked with a cross.
Results: When subtracting the BOLD effect of the control task from the effect of the main task, we have found several cerebellar areas, specifically left cerebellar lobule 6, left cerebellar lobule 8 and vermis 8.
Conclusion: Our results suggest that the left cerebellar hemisphere, mainly lobule 6 and 8, plays an essential role in motor timing, in accordance with the notions in the growing body of different research projects.
Disclosure: Nothing to disclose

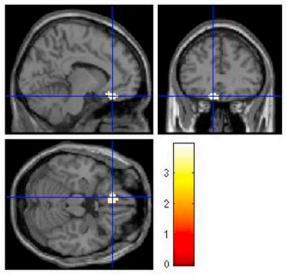
P4170

Representation of self-relevant motor information in ventromedial prefrontal cortex (vmPFC) in patients with functional conversion disorders (preliminary results)

S. Galli[1], S. Aybek[2], R. Blakemore[2], I. Sinanaj[2], T. Moulin[1], P. Vuilleumier[2]
[1]*Department of neurology, Besançon, France,* [2]*Laboratory for behavioral neurology and imaging of cognition, Geneva, Switzerland*

Background and aims: Abnormal activation in the vmPFC has repeatedly been observed in functional neurological disorders (FNDs). Our aim is to test with fMRI for differential activation patterns in the vmPFC in motor FNDs during the visual presentation of stimuli (words) that call for motor or bodily representations relevant to the self.
Methods: Patients saw different word categories that include neurological symptoms relevant or not (e.g. paralysis or tremor), respiratory symptoms, motor bodily parts, respiratory parts, and a neutral word category. A second-level flexible factorial model was used with the following contrasts: motor bodily symptoms and/or motor bodily parts relative to the respiratory ones, and self-relevant versus non-relevant motor symptoms. A region of interest (ROI) analysis was performed for the vmPFC as determined by a separate localiser task using „self" processing. Peaks at $p<0.001$ uncorrected with a number of voxels ≥ 10 were considered significant.
Results: 12 patients with motor FNDs were tested including 8 with deficit, 3 with abnormal movement, and 1 with both. The rectal orbitofrontal gyrus and posterior vmPFC were selectively reduced in response to words related to the motor system (body part & symptom), as compared to the respiratory system. These changes partly overlapped with a self-related ROI in vmPFC.

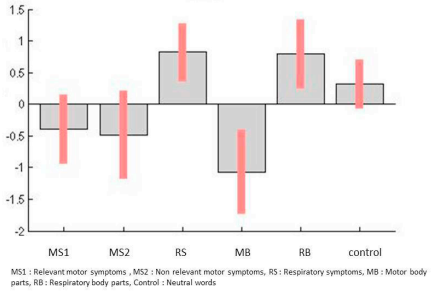
Fig 1 : Motor system (symptom & body part) < respiratory system



MNI coordinates : -9, 32, -20, p < 0.001 uncorrected, number of voxels > 9

Contrast between motor and respiratory system

Fig 2 : VmPFC activation by each condition



MS1 : Relevant motor symptoms , MS2 : Non relevant motor symptoms, RS : Respiratory symptoms, MB : Motor body parts, RB : Respiratory body parts, Control : Neutral words

VmPFC activation by each condition

Conclusion: VmPFC activity decrease during the evocation of motor symptoms and body parts in FNDs, which may reflect a reduction in self attribution processes operating on motor and body related signals which may contribute to the symptom. Comparison with a control group with organic motor symptoms will be important.
Disclosure: Nothing to disclose

P4171

Widespread abnormalities of brain connectivity in patients with glaucoma

A. Giorgio, P. Frezzotti, F. Toto, A. De Leucio, S.A. Bagaglia, N. De Stefano
University of Siena, Sienna, Italy

Background and aims: Glaucoma is an important cause of irreversible blindness worldwide. Recent quantitative MRI studies showed that these patients can have damage in brain areas of the visual system. However, it is not clear whether brain changes also occurs beyond the visual system

Methods: We performed multimodal MRI in 105 subjects (patients with different glaucoma stages [n=76] and age-matched normal controls [NC, n=29]). We used imaging tools from FMRIB Software Library (Oxford, UK) such as: i) tract-based spatial statistics for assessing diffusion tensor imaging-based anatomical connectivity across white matter (WM) tracts, and ii) independent component analysis followed by individual timecourse regression for evaluating functional connectivity within the different resting state networks. A nonparametric permutation testing, $p<0.005$ uncorrected, $k>30$ voxels was used for voxelwise statistics across the brain.

Results: Compared to NC, patients with glaucoma showed altered anatomical connectivity (i.e., reduced fractional anisotropy and increased axial diffusivity) not only along the visual pathway (optic radiations [inferior frontooccipital and longitudinal fascicles] and optic tracts) but also in non-visual WM tracts (superior longitudinal fascicle, forceps major and minor, WM of the frontal gyrus, planum temporale and postcentral gyrus) ($p<0.001$ for all). Moreover, functional connectivity was lower in patients with glaucoma than in NC in the visual network, working memory network and default mode network ($p<0.001$ for all).

Conclusion: These findings suggest that a classically vision disorder such as glaucoma has a widespread neurological involvement characterized by diffuse abnormalities in both anatomical and functional connectivity of the brain.

Disclosure: Nothing to disclose

Neuro-ophthalmology/neuro-otology 2

P4172

Bilateral persistent otolith dysfunction in benign paroxysmal positional vertigo

S.-Y. Oh[1], E.-J. Kim[2], J.S. Kim[3], B.-S. Shin[4]
[1]Jeonju city, Korea, Republic of, [2]Chonbuk National univesity hospital, Jeonju, Korea, Republic of, [3]Seoul National University Bundang Hospital, Seoul, Korea, Republic of, [4]Chonbuk National , Jeonju, Korea, Republic of

Background and aims: The objective of this study was to evaluate utricular and saccular function depending on the subtypes and therapeutic results of benign paroxysmal positional vertigo (BPPV) using ocular and cervical vestibular evoked myogenic potentials (VEMPs) during the acute and resolved state after repositioning maneuvers.

Methods: Patients diagnosed with BPPV involving the vertical and horizontal semicircular canals (n=112) and normal controls (n=35) were included. Ocular and cervical VEMPs (oVEMP and cVEMP) to air-conducted sound (ACS; 1000 Hz tone burst, 125 dB Sound pressure level [SPL]) were measured for assessment of otolith function at the time of initial diagnosis and 2 months after successful repositioning maneuvers.

Results: The prevalence of abnormalities in cVEMP or oVEMP induced by ACS in patients with BPPV was significantly higher compared to the control group ($p<0.001$). In affected ears, abnormal results were found in 47 patients (47/112, 42.0%), which included absent (31/47, 65.9%), reduced (6/47, 12.8%), and delayed responses (25/47, 53.2%). Results from non-affected ears of BPPV patients also showed frequent abnormal VEMP responses. Compared to the cVEMP findings, oVEMP abnormalities in the BPPV group were more frequent in both affected and non-affected ears (33.6% in oVEMP vs. 17% in cVEMP, at the affected ear, $p=0.003$). The abnormal VEMPs did not recover after successful repositioning therapies.

Conclusion: This result suggests that degenerative pathological changes of the saccular macular and more likely utricular macular in patients with idiopathic BPPV may cause bilateral and persistent VEMP abnormalities after repositioning maneuvers.

Disclosure: Nothing to disclose

P4173

Trans-synaptic degeneration in neuromyelitis optica spectrum disorder - evidence of brain parenchymal alterations associated with retinal damage

F. Pache[1], H. Zimmermann[2], S. Papazoglou[1], A. Lacheta[1], F. Magerstädt[1], K. Ruprecht[3], A. Brandt[2], J. Wuerfel[4], M. Scheel[5], F. Paul[1]
[1]Charité, NeuroCure Clinical Research Center, Berlin, Germany, [2]NeuroCure Clinical Research Center, Berlin, Germany, [3]Charité, Department of Neurology, Berlin, Germany, [4]University Medicine Goettingen, Institute of interventional and diagnostic Neuroradiology, Goettingen, Germany, [5]Charité, Department of Radiology, Berlin, Germany

Background and aims: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the CNS characterized by potentially devastating optic neuritis (ON) and myelitis. Data suggesting cerebral involvement in NMOSD is scarce. Here, we investigate brain parenchymal integrity alterations in NMOSD and their association with retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thinning.

Methods: 21 patients with NMOSD and 21 sex and age matched healthy control (HC) subjects were enrolled. All participants underwent extensive 3T MRI and spectral domain OCT examinations with RNFL and GCL analysis. DTI was analyzed by Tract Based Spatial Statistics (TBSS).

Results: The cohort comprised 21 NMOSD patients including two testing sero-negative for AQP-4 antibodies (90.5 % seropositive). Unilateral optic neuritis (ON) occurred in 27 cases (64%), and 9 patients reported ON of both eyes (42 %). OCT analysis showed a marked reduction of both RNFL and GCL in NMOSD compared to HC.

DTI analysis revealed significantly reduced fractional anisotropy (FA) of the optic radiation (OR) in NMOSD compared to HC. Reduced FA correlated with RNFL thickness.

Conclusion: ON is reflected by structural abnormalities of the OR in NMOSD patients, presumably caused by trans-synaptic degeneration within the visual pathway subsequent to ON.

Disclosure: FlP, KR, JW and FrP are supported by the German Ministry of Education and Research (BMBF/ KKNMS, Competence Network Multiple Sclerosis). Dr. J. Wuerfel serves on advisory boards for Novartis and Biogen Idec. He received a research grant from Novartis, and speaker honoraria from Bayer, Novartis, Teva and Biogen Idec.

P4174

Activation of prefrontal cortex in complex postures: a near-infrared imaging study

I. Pulido-Valdeolivas[1], D. Gómez-Andrés[2], C. Pradhan[3], R. Schniepp[4], K. Jahn[5], S. Glasauer[3]
[1]Universidad Autónoma de Madrid, Anatomy, Histology and Neuroscience, Madrid, Spain, [2]Hospital Universitario La Paz, Pediatric Neurology, Madrid, Spain, [3]University of Munich, Center for Sensorimotor Research, Munich, Germany, [4]University of Munich, Department of Neurology, Munich, Germany, [5]University of Munich, German Center for Vertigo and Balance Disorders (DSGZ), Munich, Germany

Background and aims: Posture control has predominantly been linked to subcortical structures based on animal studies. Hence, balance problems in humans are usually believed to depend on subcortical deficits. However, recent studies suggest that cortical areas are involved in postural responses to external perturbations. The aim of this work is to demonstrate the activation of the frontal lobe during the tandem-Romberg test (tR), an internally-perturbed, complex posture commonly used in clinical examinations.

Methods: In 19 healthy volunteers, changes of oxyhemoglobinewere measured over time in the superficial frontal lobe during 3 different sequences of tasks (figure C): stance with open and closed eyes (OE/CE), stance with OE and tR with CE, and stance with CE and tR with CE. A 22-channel 3x5 array (8emitters/7receptors) and 30 mm inter-optode distance (Hitachi ETG4000) was placed (reference Fpz, figures A&B). After a wavelet-based and hemodynamic response function filtering, a general linear model was used to contrast differences in oxyhemoglobine between tasks.

Results: A significant activation was found in channels that measured in bilateral dorsolateral and frontopolar cortices (Brodmann's areas 10 and 46) of the middle and frontal gyri, in the second and third sequences of tasks (figure C) during tR with higher signal when the task wasfully done with CE.

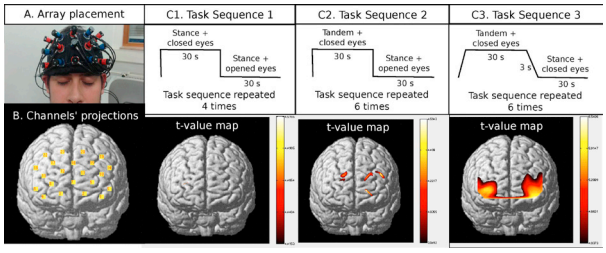


Figure A, B and C

Conclusion: Dorsolateral and frontopolar cortices are recruited in the maintenance of internally-perturbed, complex postures. Clinical tests that were previously thought to be assessing only subcortical structures might therefore test a cortical-subcortical network devoted to balance control, in which the frontal lobe plays a prominent role.

Disclosure: This study was supported by the BMBF (DSGZ, grant 01EO1401) and by the DFG (Graduate School for Systemic Neuroscience).

P4175

Real-time computer based visual feedback improves visual acuity in downbeat nystagmus – a pilot study

J. Teufel[1], S. Bardins[1], O. Kremmyda[1], M.L. Strupp[1], R. Kalla[2]
[1]University of Munich (Großhadern), Munich, Germany, [2]Inselspital Bern, Neurologie, Berne, Switzerland

Background and aims: Patients with downbeat nystagmus syndrome suffer from oscillopsia, which leads to an unstable visual perception and therefore impaired visual acuity. The aim of this study was to use real-time computer based visual feedback to compensate for the destabilising slow phase eye movements.

Methods: The patients were sitting in front of a computer screen with the head fixed on a chin rest. The eye movements were recorded by an eye tracking system (EyeSeeCam®). We tested the visual acuity with a fixed Landolt C (static) and during real-time feedback driven condition (dynamic) in gaze straight ahead and (20°) sideward gaze. In the dynamic condition, the Landolt C moved according to the slow phase eye velocity of the downbeat nystagmus.

Results: 10 patients with downbeat nystagmus were included in the study. Median age was 76 years and the median duration of symptoms was 6.3 years. The mean slow phase velocity was moderate during gaze straight ahead (1.44°/s, SD±1.18°/s) and increased significantly in sideward gaze (mean left 3.36°/s; right 3.58°/s). In gaze straight ahead, we found no difference between the static and feedback driven condition. In sideward gaze, VA improved in five out of ten subjects during the feedback-driven condition (VA 0.1; Mann-Whitney-U-Test p=0,032).

Conclusion: We found an improvement of visual acuity in sideward gaze during the feedback driven condition. Therefore, real-time visual feedback may be a promising aid for patients suffering from oscillopsia and impaired text reading on screen, but further research is needed.

Disclosure: Nothing to disclose

P4176

Noisy galvanic vestibular stimulation improves dynamic walking stability in healthy subjects

M. Wuehr, E. Nusser, S. Krafczyk, T. Brandt, K. Jahn, R. Schniepp

University of Munich, German Center for Vertigo and Balance Disorders, Munich, Germany

Background and aims: We examined the effect of galvanic vestibular stimulation (GVS) delivered as zero-mean white noise current (noisy GVS) on the walking performance in healthy subjects.

Methods: The walking performance of 15 healthy subjects (mean age 23.0±1.3 years) at slow, preferred and fast walking speed was examined during two different conditions: (1) walking with eyes closed and zero amplitude sham noisy GVS, and (2) walking with eyes closed and non-zero amplitude noisy GVS set to 80% of the individual sensory threshold for GVS. We examined 10 gait parameters: stride time, stride length, base of support, swing time percentage, double support time percentage as well as the CV of stride time, stride length and base of support, gait asymmetry and bilateral phase synchronization.

Results: Noisy GVS significantly improved stride time CV by 34% ($p<0.019$), stride length CV by 26% ($p<0.048$), base of support CV by 18% ($p<0.004$), gait asymmetry by 39% ($p<0.037$), and bilateral phase synchronization by 19% ($p<0.042$). This ameliorating effect of noisy GVS on locomotion function was only observable during slow walking speeds.

Conclusion: Noisy GVS is effective in improving locomotion function in healthy subjects. It predominantly targets the variability and bilateral coordination characteristics of the walking pattern, which are critically linked to dynamic walking stability. The predominant impact of noisy GVS during slow walking supports the principle of a speed-depended role of sensory feedback in locomotion control.

Disclosure: Nothing to disclose

P4177

Correlation between the bedside and video head impulse test

C.W. Yip[1], M. Strupp[2]

[1]National Neuroscience Institute (SGH Campus), Neurology, Singapore, Singapore, [2]University Munich, Department of Neurology, Munich, Germany

Background and aims: The bedside head impulse test (bHIT) rapidly assesses the function of the high-frequency vestibular-ocular reflex (VOR). This study compares the findings of the bHIT with the video HIT (vHIT) as the gold standard.

Methods: The double-blinded study prospectively enrolled all patients who presented with vertigo or dizziness as a chief complaint from a tertiary vertigo centre. Three experienced clinical raters performed the bHIT and documented their findings separately. The vHIT was done with the otometrics video HIT system, at the end of the patient visit.

Results: 404 patients were examined in a standardized way. 2056 bHITs and 808 vHITs were performed. With a cut-off value for a normal VOR gain of 0.7 the bHIT's mean sensitivity was 63%, mean specificity 84.4%, mean positive predictive value (PPV) 43.9%, and mean negative predictive value (NPV) 92.8%. With a vHIT VOR gain of 0.65 the bHIT's sensitivity was 68.6% and with a vHIT VOR gain of 0.6 it was 75.7%. Inter-rater variability was moderate.

Conclusion: (i) The bHIT was only moderately sensitive with a poor PPV even with experienced physicians to diagnose VOR deficits; (ii) however, with a vHIT gain cut-off value of 0.60 the majority of clinically relevant cases can be diagnosed; (iii) a normal bHIT has good specificity in experienced hands and detects >90% of the negative cases; (iv) the vHIT is a very useful clinical tool to quantify vestibular function.

Disclosure: Nothing to disclose

P4178

Correlation between dizziness handicap inventory (DHI) and vestibular function in patients with persistent peripheral vestibular disorders.

C.W. Yip[1], M. Strupp[2]
[1]National Neuroscience Institute (SGH-Campus), Neurology, Singapore, Singapore, [2]University Munich, Department of Neurology, Munich, Germany

Background and aims: Patients suffering from peripheral vestibular disorders may complain of persistent impairment in daily activities. They have abnormal vestibular function tests, and clinicians often use these results exclusively to explain the patients' disability. The applicability of this cause-and-effect approach has not been studied. We aim to test this assumption by correlating the patient-reported disability using the Dizziness Handicap Inventory (DHI) with various vestibular test parameters.

Methods or Materials or Case Report: Patients with persistent vestibular complaints due to a previously diagnosed peripheral vestibular disorder without evidence for central or functional dizziness were prospectively recruited from a tertiary vertigo centre. The diagnoses included: Menière's disease, post vestibular neuritis, BPPV, vestibular paroxysmia, and bilateral vestibulopathy. They underwent at least 3 of the following laboratory tests: bithermal binaural caloric testing, video head impulse testing (vHIT), cervical and ocular vestibular evoked myogenic potentials, and static posturography. In addition, they filled out the DHI.

Results: In 60 patients, the DHI was correlated with each individual test parameter (VOR gain, unilateral weakness on calorics, cVEMP/oVEMP for saccular/utricular function, sway paths on fixed and foam surface). None of these parameters were significantly correlated with the DHI.

Conclusion: This study suggests that abnormalities found in vestibular function tests, regardless of their severity, do not correlate with the DHI scores. Therefore, the clinician must be cautious and put vestibular testing into perspective when treating patients with persistent dizziness. So far únquantifiable patient factors may be more important in determining the level of disability than the results of vestibular tests.

Disclosure: Nothing to disclose

P4179

Retinal damage in MOG-antibody-positive neuromyelitis optica spectrum disorder phenotype patients

H.G. Zimmermann[1], J. Mikolajczak[1], A. Lacheta[1], F. Magerstädt[1], K. Ruprecht[2], F. Paul[1], A. Brandt[1], F. Pache[1]
[1]Charité University Medicine, NeuroCure Clinical Research Center, Berlin, Germany, [2]Charité University Medicine, Clinical and Experimental Multiple Sclerosis Research Centerand Department of Neurology, Berlin, Germany

Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are a group of neuro-inflammatory disorders characterized by longitudinally extensive transverse myelitis and/or optic neuritis. About 70% of patients with a NMOSD phenotype have antibodies to the astrocytic water channel aquaporin (AQP)-4. Recently, antibodies to myelin oligodendrocyte glycoprotein (MOG) were discovered in a subset of patients with a clinical phenotype of NMOSD but without AQP4-antibodies. Here, we describe retinal damage in a series of MOG-antibody-positive patients displaying an NMOSD phenotype.

Methods: Retrospective analysis of four MOG-antibody-positive patients (all female, age 19 - 77 years). None of the patients had AQP4-antibodies. Study data included optic neuritis (ON) relapse history, optical coherence tomography of the peri-papillary retinal nerve fibre layer (RNFL) and the macula, visual acuity and visual evoked potentials.

Results: 3 patients had a history of ON in both eyes, 1 patient had no history of ON. In 5 of 6 ON eyes, ON was recurrent and presented with prolonged or absent P100 latencies. 3 eyes of 2 patients were blind. RNFL thickness was severely reduced in ON eyes (53±18µm) with 5 of 6 eyes in the lowest 1% percentile of the reference database. Macular microcysts were found in 2 eyes of 2 patients. 1 patient presented with dynamic macular microcyst changes over a three-year follow-up.

	Patient 1	Patient 2	Patient 3	Patient 4
Age / years	54	54	77	19
ON history	Bilateral, recurrent	Bilateral, recurrent	Bilateral, OD recurrent, OS isolated	no ON
Macular microcysts	OD	OS	*none*	*none*
OD RNFL / µm	42	38	47	84
OD Visual Acuity	20/20	*blind*	*blind*	20/16
OD VEP P100 Latency / ms	138	140	N/A	95
OS RNFL / µm	65	44	85	87
OS Visual Acuity	20/20	*blind*	20/25	20/16
OS VEP P100 Latency / ms	134	*blind*	107	93

Overview of demographic data, retinal morphology, visual acuity and VEP results of the included subjects. Abbreviations: ON: optic neuritis; RNFL: retinal nerve fibre layer; VEP: Visual evoked potential

Conclusion: Albeit MOG-antibody-positive patients were shown to experience fewer attacks and better recovery than AQP4-antibody-positive NMOSD patients in earlier studies, this case series shows that retinal damage and thus visual dysfunction can be devastating.

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Sleep disorders 2

P4180

Sleep disorders after traumatic brain injuries

B. Carlan[1], S. Diaconu[2], R. Mircea[3], A. Voina[3], S. Paripas[3], M. Moarcas[2], O. Deleanu[4], D.C. Jianu[5], C. Falup Pecurariu[6]
[1]Faculty of Medicine, Transilvania University Brasov, Brasov, Romania, [2]Emergency Clinical County Hospital Brasov, Neurology, Brasov, Romania, [3]Emergency County Hospital Brasov, Neurosurgery, Brasov, Romania, [4]University of Medicine and Pharmacy „Carol Davila", Bucharest, Romania; National Institute of Pneumology „Marius Nasta", Pneumology, Bucharest, Romania, [5]County Emergency Hospital, Victor Babes University of Medicine and Pharmacy, Neurology, Timisoara, Romania, [6]Brasov, Romania

Background and aims: Traumatic brain injuries (TBI) have several immediate and long-term consequences on quality of life. The aim of this study is to assess the prevalence and effects of traumatic brain injury on sleep.

Methods: Prospective study of 41 patients with traumatic brain injury. Evaluation was done using Glasgow Coma Scale (GCS), Athens Insomnia Scale, Insomnia Severity Index (ISI), Berlin Questionnaire for Sleep Apnea, Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS).

Results: There were 28 men (68.29%), with the mean age of 43.5±17.26 years. The most frequently encountered sleep disorder following TBI was insomnia (n=15; 37%). Excessive daytime sleepiness (n=14; 34%) was considered when Epworth Sleepiness Scale score was higher than 10. Nine patients reported suggestive symptoms of sleep apnea. Less frequently reported were circadian rhythm disturbances. 27 patients (68.85%) experienced mild daytime dysfunction due to poor quality of sleep (PSQ>5) and 69.69% of patients reported fatigability. There was correlation between severity of insomnia and daytime functioning impairment (p=0.03). Excessive daytime sleepiness was also correlated with loss of consciousness (p=0.008).

Conclusion: Sleep disorders represent important consequences of traumatic brain injuries and need careful assessment due to the significant negative impact of patient's quality of life.

Disclosure: Nothing to disclose

P4181

A pilot study on the localization of symptoms in Restless Legs Syndrome (RLS)

F. Rinaldi[1], M. Zucconi[2], A. Oldani[2], S. Marelli[2], A. Galbiati[2], M. Cusmai[2], A. Gasperi[2], L. Ferini Strambi[2]
[1]Università degli Studi di Brescia, Spedali Civili di Brescia, Neurology, Brescia, Italy, [2]San Raffaele Scientific Institute, Dept of Clinical Neurosciences, Sleep Disorders Center, Milan, Italy

Background and aims: The accepted diagnostic criteria for RLS describe the symptoms as confined mainly to the legs. Nevertheless, in daily practice an amount of patients report symptoms also in the upper limbs. Our aim was to describe the topography and symmetry of RLS symptoms, identifying the relationship between localization and clinical variables.

Methods: 146 RLS patients were studied. Information including localization of symptoms, age-at-onset, ferritin values and symptoms severity were collected. The RLS topography patterns were classified according to localization in upper limbs (UL), lower limbs (LL) or both, and lateralization.

Results: Bilateral and symmetric lower limbs (LL) location was the most common (74.7 %), while 4.1% exhibited asymmetric lower limbs localization. 1 patient (0.7%) showed symptoms confined to the upper limbs (UL), symmetrically. 4 limbs symmetrical involvement was found in 17.8% of patients; symptoms were located asymmetrically at the 4 limbs in 2.7%. The severity of RLS was similar across the patients, independently of the localization of symptoms. Conversely, lower ferritin values were found in patients with symptoms located at the lower limbs. Patients with asymmetric symptoms had a younger age-at-onset; nevertheless, the numerosity of the two samples was skewed, therefore an extended sample is needed to assess the statistical significance.

Conclusion: RLS symptoms were typically in the lower extremities and symmetrical. LL patients had higher ferritin values, while patients with a younger age-at-onset showed more asymmetric distribution compared with older ones. A larger sample of patients is needed in order to ascertain the significance of this findings.

Disclosure: Nothing to disclose

P4182

A clinical and polysomnographic study defining the phenotype of restless legs syndrome (RLS)

F. Rinaldi[1], M. Zucconi[2], A. Oldani[2], S. Marelli[2], A. Galbiati[2], M. Cusmai[2], A. Gasperi[2], L. Ferini Strambi[2]
[1]Università degli Studi di Brescia, Spedali Civili di Brescia, Neurology, Brescia, Italy, [2]San Raffaele Scientific Institute, Dept of Clinical Neurosciences, Sleep Disorders Center, Milan, Italy

Background and aims: Idiopathic and secondary RLS can have a familial component. Younger age-at-onset in familial and idiopathic cases has been previously found, with conflicting results. We aimed to determine the clinical and polysomnographic characteristics of a cohort of RLS patients.

Methods: 400 RLS patients were studied, including information on age-at-onset, comorbidities, familial history, time of symptoms onset and the presence of impulse control behaviours (ICBs).

Results: Mean age-at-onset differed as a function of presence/absence of a familial history of RLS (40.44 years±16.43 vs. 49.03 years±15.33, p=0,00). Clinical and polysomnographic characteristics were similar in both groups, but WASO was significantly longer in familial RLS (123.18 min±80.14 vs 91.65 min±96.36, p=0.019). No difference was found for the age-at-onset between idiopathic and secondary RLS (44.89 years±16.35 vs. 45.02 years±16.64, p=0.94). PLM index was higher in idiopathic RLS (145±44.65 vs. 83±31,91, p= 0.026). Time of onset of symptoms was in the evening or at bedtime in 28.04% and 37.80% of patients respectively, but in 21.34% of patients onset was >1 h after sleep onset. ICBs were found in 23/173 RLS patients on dopamine agonist (DA) therapy.

Conclusion: Our analyses support the hypothesis that RLS is divided into early and late onset disease, but with smaller difference than previously reported. A high percentage of patients showed a time of symptoms onset after sleep onset. RLS patients treated with DA showed higher risk of ICBs than previously reported.

Disclosure: Nothing to disclose

P4183

Patients with insomnia and with obstructive sleep apnoea performing a visual search task

E. Giora, A. Galbiati, S. Marelli, L. Ferini Strambi
San Raffaele Scientific Institute, Dept of Clinical Neurosciences, Sleep Disorders Center, Milan, Italy

Background and aims: Although there is a huge evidence of how acute sleep deprivation affects cognitive functions, little is known about the effects of chronic sleep diseases on visual perception. The aim of this research is to test the efficiency of visual processing in insomnia and Obstructive Sleep Apnoea (OSA) patients. Visual efficiency was tested by means of a visual search paradigm.

Methods: Participants had to detect the presence/absence of a target (letter T) embedded into a set of characters (letters Os, Xs, Ls, respectively). The test-stimuli were presented without time constraints and subjects had to perform the two-alternative-forced-choice task as soon as possible. The saliency of the target with respect to the contextual letters (T vs. Os, Xs, or Ls, respectively) and the distractors' number (15, 30, 60) were manipulated. As dependent variables, accuracy and reaction times were recorded. The results of 24 insomnia (mean age: 47±14 years) and 22 OSA (mean age: 51±11 years) patients were compared with the performance obtained by 22 control subjects (mean age: 45±14 years).

Results: While no difference was observed in accuracy, an overall increase of response latency was found in both clinical groups compared to control subjects. However, while the difference in reaction times between OSA patients and controls was constant for all stimuli, insomniacs showed a selective higher impairment for the more difficult conditions.

Conclusion: Those results indicate an overall reduced visual efficiency in populations suffering from sleep disorders and an additional impairment for insomniacs when performing effortful visual search tasks.

Disclosure: Nothing to disclose

P4184

Partnership and sexual dysfunction in narcolepsy

H. Hidalgo Pareja[1], J. Mathis[2], D. Hidalgo[1], C. Bassetti[2], U. Kallweit[2]

[1]Katzenelnbogen, Germany, [2]Berne, Switzerland

Background and aims: Narcolepsy with cataplexy (NC) is a chronic neurological disorder affecting approximately 0.02% of the population worldwide. Little is known on the consequences of partnership and sexuality of concerned patients. We present an interim analysis of our study on sexual dysfunction in NC aiming at assessing its frequency, severity and impact on patient's life.

Methods: Consecutive NC patients treated at the sleep-wake center Rhine-Lahn, Katzenelnbogen, Germany were included. Assessment was performed by using a detailed self-issued questionnaire about partnership and sexual functioning.

Results: Up to now, 92 NC patients, aged between 18 and 77 years, 47 of them women (61%) were included. 77 (83%) completed the questionnaire on partnership and sexuality. Out of 77 NC patients, 30 (38%) had no partner. Narcolepsy led to failure of a partnership in 16%, problems in partnership due to narcolepsy were described as "serious" in 25%, "sometimes" in 45%. Most impairing symptom was excessive daytime sleepiness in 78%. Discontent with sexuality was described in 53%; most stressing symptoms were sleepiness (48%), and cataplexy (22%). Lack of sexual interest was described in 49%; libido was reduced or vanished in 57%. 40% rated this complaint as side effect of medication. Orgasmolepsy occurred in 42% (9% "always").

Conclusion: Sexual dysfunction in NC is frequent. Most annoying symptoms for partnership and sexuality were EDS, and to some extend cataplexy and orgasmolepsy. Restrictions in partnership and sexual life caused by diseases symptoms and medication should be observed in the treatment of narcoleptic patients.

Disclosure: Nothing to disclose

P4185

Delayed sleep phase may predispose to multiple nocturnal seizure occurrences in epilepsy

S. Khachatryan[1], T. Stepanyan[2], L. Ghahramanyan[1], A. Karamyan[1]

[1]Somnus Sleep and Movement Disorders Clinic, Yerevan, Armenia, [2]Erebouni MC, Republic Epilepsy Center, Yerevan, Armenia

Background and aims: Sleep complaints and disorders are frequently encountered in patients with epilepsy (PWE). Circadian rhythm sleep disturbances (CRSD), especially delayed sleep phase (DSP) type, are frequent in general population, but poorly studied in epilepsy. The aim of our study was to assess association between CRSD and nocturnal seizures.

Methods: Adult patients with epilepsy diagnosis proven at a tertiary epilepsy center were enrolled in the study, and classified into partial epilepsy (PE) and generalized epilepsy (GE) types according to simple conventional approach. Two types of CSR patterns were defined for this study: normal sleep rhythm (NSR) - fall asleep before 2AM, DSP - fall asleep after 2AM. Nocturnal seizure occurrence and multiple seizures per night cases were recorded and analyzed. Chi square test was used for statistical analysis.

Results: We included 150 PWE, aged 18-71, mean age - 34.3; 64 females (42.7%). Of them 128 (85.3%) had NSR, and 22 (14.7%) had DSP. Of the sample, PE comprised 76.9%, GE – 23.1%. There was no difference in nocturnal seizure occurrences between NSR and DSP. However, we found significantly more patients at risk of having frequent nights with 2 and more seizures in GE patients with DSP type (15.4%) compared to PE (3%), $p<0.05$.

Conclusion: Our data suggest that although nocturnal seizures are not dependent on CRSD in our general sample, GE patients with CRSD of DSP type are more prone to have multiple seizures per single night than PE patients.

Disclosure: Nothing to disclose

P4186

Study of the sleep pattern in patients with ischemic cerebrovascular stroke

J. Mekky[1], D. Elsalamawy[2], O. Elkholy[3], N. Hafez[3]
[1]Alexandria, Egypt, [2]Faculty of Medicine, Neuropsychiatry , [3]Alexandria university, Neuropsychiatry, Alexandria, Egypt

Background and aims: Cerebrovascular stroke is a common neurological disorder with many sequale, one of these underrecognised complications are sleep disorders.The aim of this study is to evaluate the sleep pattern in these patients following teir first ischemic stroke,taking into consideration the site and size of the lesion.

Methods: 93 patients with the first ischemic stroke ,admitted to the ICU subjected to initial assessment with the Pittsburgh sleep index and then one month later. After one month an overnight polysomnography was performed to all the patients, and a matched control groupof 50 persons.

Results: There was a significant difference between pateints and control, as regards the total sleep time and latency which were longer in patients. Meanwhile the sleep efficiency was less and REM sleep duration were significantly shorter in the patient group. The sleep indices especially the arousal index, the Limb Movement Index were higher in the pateint group.In addition to that all the respiratory sleep indiced were significantly higher in the stroke patients, including the snoring index, apnea hypopnea index and desaturation index. The stroke site affected only the REM sleep, while the stroke size was positively correlated to the desaturation index and the lowest oxygen saturation during the polysomnography.

Conclusion: Different sleep disorders may appear following a stroke, this will directly affect the patients morbidity. Neurologists should pay attention to the patient sleep complain and screen unrecognised sleep related breathing disorders as an example.The prompt treatment of these disorders will improve the outcome and qulity of life of patients.

Disclosure: Nothing to disclose

Movement disorders 10

P4201

Clinical impact of turnover during sleep quantitatively evaluated by accelerometer in patients with Parkinson's disease

M. Akamatsu, M. Shiraishi, K. Uchino, F. Maki, A. Tsuruoka, S. Tanaka, D. Hara, Y. Hasegawa
St.Marianna University School of Medicine, Department of Internal Medicine Division of Neurology, Kawasaki, Japan

Background: To elucidate impact of motor complications during sleep in patients with Parkinson's disease, we quantitatively evaluated turnover during sleep by accelerometer and related with UPDRS and sleep quality scales.

Methods: In 25 PD patients and 7 control subjects, turnover movements were continuously monitored during sleep by using three-axis accelerometer. Turnover was identified by specific signal changes on the three axis (>0.25G). Sleep quality was evaluated by using the Epworth Sleepiness Scale (ESS) and the Parkinson's Sleep Scale-II (PDSS-II). We also investigated changes in the number of turnover movements and serum levodopa concentrations after administration of levodopa-carbidopa (50mg) at 6:00pm and 9:00pm.

Results: The number of turnover during sleep in PD patients and control subjects were 4.9±6.0 and 21.4±17.0, respectively (p=0.005). The number of turnover was significantly correlated with age (r=0.103, p=0.028), ESS (r=-0.322, p=0.040), and PDSS-II (r=-0.350, p=0.048). The number of turnover in PD patients with 3rd tertile of UPDRS (>57) was significantly smaller than that in controls. Additional levodopa administration increased the number of turnover from 4.9±4.3 to 6.9±4.8, however, these changes were not correlated with serum levodopa concentrations.

Conclusion: Turnover movements in PD patients with high UPDRS score were significantly restricted and decreased turnover movements were associated with their daytime sleepiness. Monitoring of motor complications during sleep in PD patients by accelerometer is feasible and may be useful to improve their QOL.

Disclosure: Nothing to disclose

P4202

Usefulness of transcranial ultrasound in atypical parkinsonism: a cross-sectional study

A. Alonso-Canovas[1], J.L. Lopez-Sendon[1], A. DeFelipe-Mimbrera[1], M.C. Matute-Lozano[1], S. Sainz de la Maza-Cantero[1], R. Alvarez-Velasco[1], J. Buisan[1], G. Garcia-Ribas[1], I. Aviles-Olmos[1], J. Masjuan Vallejo[2], J.C. Martinez-Castrillo[1]
[1]Hospital Universitario Ramon y Cajal, Neurology, Madrid, Spain, [2]Hospital Ramón y Cajal, Neurology, Madrid, Spain

Background and aims: Atypical Parkinsonian Syndromes (APS) diagnosis is challenging. Transcranial Ultrasound (TUS) has proven useful in Parkinson's Disease (PD) and a building evidence indicates a potential role in APS.

Methods: Analysis of clinical and sonographic features of patients with progressive supranuclear palsy-PSP, multiple system atrophy-MSA, and corticobasal degeneration-CBD. Clinical diagnosis was established following consensus criteria. TUS criteria for APS (substantia nigra-SN and lenticular nucleus-LN echogenicity, III ventricle-IIIV amplitude) were applied by an experienced sonographer and findings compared with 105 PD patients and 138 controls (C).

Results: 22 patients with APS (63.6% male, 73±10 years) underwent TUS. Clinical diagnosis was PSP in 9, MSA in 8, CBD in 1, overlapping syndromes in 4. Two patients (9.1%) had billaterally absent transtemporal bone window. In the remaining 20, TUS showed atypical findings in 18 (90%) and typical PD findings in 2 (10%). Clinical and ultrasound diagnoses were concordant in 15 cases (5 MSA, 9 PSP, 1 CBD), and discordant in 1 (clinical CBD, TUS PSP); 2 patients had parkinsonism without TUS abnormalities. There was SN hyperechogenicity in 40% of APS patients (83,3% of PD, p<0.0001; 10% of C, p:0.0022), LN hyperechogenicity in 63% (20.5% PD, p:0.0005; 6.8% C, p:0.0001), and enlargement of the IIIV in 40% (24.7% PD, NS; 11.5% C, p:0.0001).

Conclusion: TUS showed significantly distinct features in our APS patients when compared with PD and control subjects. TUS seems a reliable tecnique in APS diagnosis when applied by skilled sonographers following consensus criteria.

Disclosure: Nothing to disclose

P4203

Drug induced parkinsonism: can transcranial ultrasound predict response to withdrawal of the offending drug?

A. Alonso-Canovas[1], J.L. Lopez-Sendon[1], A. DeFelipe-Mimbrera[1], M.C. Matute-Lozano[1], S. Sainz de la Maza-Cantero[1], J. Buisan[1], N. Garcia-Barragan[1], I. Corral[1], J. Masjuan Vallejo[2], J.C. Martinez-Castrillo[1]

[1]Hospital Universitario Ramon y Cajal, Neurology, Madrid, Spain, [2]Hospital Ramón y Cajal, Neurology, Madrid, Spain

Background and aims: Drug induced parkinsonism (DIP) occurs during treatment with certain offending drugs (OD), and remits after withdrawal. Clinical response to withdrawal and SPECT-DaT scan discriminate definite-DIP and underlying Parkinson's disease (true-PD). Transcranial ultrasound (TUS) is useful in PD diagnosis, and has a potential role in DIP.

Methods: Prospective observational study of clinical and sonographic variables in subjects with possible-DIP. Definite-DIP was diagnosed upon improvement after withdrawal of the OD or normal SPECT. Standard TUS protocol was followed.

Results: 73 subjects, 63% female, 72.6 years (38-88) were included. Tremor (65%), symmetric signs (51,4%), and non-motor symptoms (82%) were common. Substantia Nigra (SN) was assessable in 65 subjects (89%) and hyperechogenic in 21 (32.4%). SPECT was performed in 29%. 66 subjects were followed after 10.1±7.2 months of withdrawal of the OD: 49 (74%) significantly improved (diagnosis definite-DIP) while 17 (26%) did not improve or worsened (true-PD). In multivariant analysis, normal SN echogenicity was significantly associated with clinical improvement ($p<0.0021$), and true-PD diagnosis with SN hyperechogenicity (p:0.0062), asymmetric parkinsonism (p:0.028), and hyposmia (p:0.016). TUS showed an 82% sensitivity, 85% specificity, and 97% negative predictive value for true-PD diagnosis. Analysis of 17 patients with available TUS and SPECT showed an 88.2% concordance [kappa 0.60±0.26].

Conclusion: TUS predicted accurately the outcome after withdrawal of the OD and was significatly associated with final diagnosis in our cohort of possible-DIP. A high negative predictive value for true-PD diagnosis supports a role of this non invasive tecnique as a screening tool in this setting.

Disclosure: Nothing to disclose

P4204

Clinically relevant benefits of safinamide in late-stage PD patients on levodopa and other PD medications

R. Anand[1], R.D. Hartman[2], V. Lucici[3], E. Forrest[3], R. Giuliani[3], M. McBride[4]

[1]St Moritz, Switzerland, [2]Neurwrite LLC, Morristown, USA, [3]Newron Pharmaceuticals SPA, Bresso, Italy, [4]Instat Consulting INC, Chatham, USA

Background and aims: Analyses were performed to determine if significant improvements for the primary endpoint (mean change in ON Time without troublesome dyskinesia), OFF Time and UPDRSIII in the 016 and SETTLE studies with safinamide (Xadago™, Zambon SpA, Italy) as add-on to levodopa in late-stage PD (LSPD) patients were clinically meaningful.

Methods: Pooled 016 and SETTLE studies were analysed using a modified Intent-to-Treat Population (mITT) based on randomized targeted doses (placebo; safinamide 50mg/day; safinamide 100mg/day) for the percentage of patients with clinically relevant improvement of ≥60min in ON and OFF Time, ≥30% on UPDRSIII, and those meeting all 3 criteria, and patients with improvement in CGIChange (CGI-C) were analysed. The differences in responder rates between treatment groups were compared using a logistic regression model (chi¯square test).

Results: The mITT Population for the Pooled Studies 016 and SETTLE included 1188 patients (safinamide 50mg/day, 217; safinamide 100mg/day, 486; placebo, 485). Statistically significant ($p<0.05$) greater proportions of patients in the safinamide 50 and 100 mg/day groups, compared to placebo (Pbo), met each of the responder criteria defined above. A significantly greater percentage of safinamide-treated patients met the most stringent criteria, i.e. improvement in ON Time, OFF Time and UPDRS III [50mg: 24.0% ($p=0.007$), 100mg: 21.6% ($p<0.001$), Pbo: 11.5%], or were rated improved on CGIC [50mg: 69.1% ($p=0.001$), 100mg: 61.7% ($p\leq0.001$), Pbo: 49.1%].

Conclusion: A statistically significant higher proportion of LSPD patients treated with safinamide as add-on to levodopa improved by a clinically relevant magnitude, compared with a placebo.

Disclosure: Nothing to disclose

P4205

Recognition of head-trunk and object motion signals at threshold levels is impaired in cervical dystonia

V. Skarlatou, D. Anastasopoulos
University of Athens, Physiology, Athens, Greece

Background and aims: Context dependent modification of postural reactions to head-trunk rotations has been shown to be deficient in cervical dystonia. As several sensory abnormalities, including impaired temporal discrimination of visual stimuli, have been described in patients, we hypothesized that derangements in head stabilization may result from failure to adequately detect incoming head posture disturbances. Intact self-motion and object-motion detection may be particularly relevant in this respect as this kind of information is almost exclusively shaped by velocity signals and depends on correct time computations.

Methods: 16 patients and 18 age-matched healthy controls were asked to recognize bidirectional head-trunk, whole-body and object motion sinusoidal signals at 0.1 Hz. Stimulus intensity was gradually increased from a subthreshold up to a clearly perceived level. Subjects used a joy-stick to indicate the occurrence and direction of perceived motion. Stimulus recognition was noted when the subject indicated for the first time both directions of motion. Subsequently, stimulus velocity was gradually reduced and subjects ceased to indicate motion when intensity fell below threshold.

Results: Patients were significantly less aware of head-trunk and object motion stimuli than normal subjects. They recognized trunk-in-space motion (head stationary, isolated neck-proprioceptive stimulus) once stimulus peak velocity attained 2º/s (controls: 1º/s, $p<0.04$). They indicated both directions of the horizontally rotating light spot (visuo-oculomotor stimulus) once peak velocity reached 0.5º/s (controls 0.25º/s, $p<0.05$). In contrast, whole-body rotations (vestibular stimulus) were correctly sensed by patients.

Conclusion: The selective impairments of head-to-trunk and object motion perception may contribute to malfunctioning head stabilization in patients.

Disclosure: Nothing to disclose

P4206

Modulation of dystonia during sleep

E. Antelmi[1], F. Raffaele[2], C.L. Scaglione[1], P. Martinelli[1], F. Provini[1], R. Liguori[1]
[1]Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy, [2]Sleep Research Centre, Department of Neurology, I.C., Oasi Institute (IRCCS), Troina, Italy

Background and aims: There is the general belief that dystonia disappears during sleep but polysomnographic (PSG) studies documenting this assumption lack. With the current study we aim to document the activity on dystonic muscles during the different sleep stages.

Methods: We prospectively recruited 20 patients suffering from idiopathic adult-onset cervical dystonia and 10 age-matched healthy voluntaries. Both patients and subjects were investigated by means of clinical interview and validated questionnaires for subjective sleep complains, excessive daytime sleepiness, sleep-related movements' disorders and mood complains. Both patients and subjects underwent PSG with standard montage plus additional superficial EMG leads placed bilaterally on the muscles of the cervical district.

Results: Patients (10 females) had a mean age of 50 years ±10, a mean disease duration of 8 years±5 and a moderate disease severity. Questionnaire-based interview failed to disclose any significant subjective sleep problems or mood disorders. When evaluating PSG recordings we found a disrupted sleep pattern with reduced sleep efficiency in the patient group. The analysis of the EMG traces from neck muscles showed that EMG activity in dystonic patients persisted throught all the night, althought showing a progressive decrease while approacching the deeper stages of sleep. Still, nearly 70% of the patients presented an improvement of the dystonic posture the morning after night-sleep.

Conclusion: Patients with dystonia had important sleep disruption but they did not report excessive daytime sleepiness. Dystonic spasms persisted during all the sleep stages, but their amplitude decreased during slow-wave sleep. Dystonia improved after night-sleep.

Disclosure: Nothing to disclose

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P4209
Abstract cancelled

P4210
Subclinical dysphagia in multiple sclerosis

Y. Beckmann[1], N. Gürgör[2], S. Arici[3], T. Kurt İncesu[1], Y. Secil[3], C. Ertekin[1]
[1]Izmir, Turkey, [2]Katip Çelebi University Atatürk Training and Research Hospital, , Neurology, Izmir, Turkey, [3]Katip Celebi University, Atatürk Training and Research Hospital,, Izmir, Turkey

Background and aims: Swallowing mechanism and neurogenic dysphagia in MS have been rarely studied by electromyographical methods. This study aims to evaluate the presence of subclinical dysphagia in patients with mild multiple sclerosis(MS) using electrophysiological methods.
Methods or Materials or Case Report: A prospective study of 51 patients with relapsing remitting MS (RRMS) and 18 age-matched healthy adults were investigated. We used electromyography to measure the activity of the submental muscles during swallowing, as well as respiration, electrocardiographic and electrodermal activity during the procedures of dysphagia limits and sequential water swallowing. Electrophysiological recordings of patients were obtained during relapse, after relapse and at any time in remission period.
Results: Clinical dysphagia was found in 12 % of MS patients while electrophysiological swallowing abnormalities were encountered in 33% of patients. Subclinical dysphagia was determined in 35% of patients during an MS relapse, in 20 % of patients after a relapse, and in 25% of all 51 patients in the remission period based on EMG findings. Duration of swallowing signal of submental muscles in all MS patients was found to be longer than in normal subjects (p=0.001). During swallowing of 50 ml of sequential water, the compensatory respiratory cycles occurred more often in MS patients than normal subjects, especially during a relapse (p=0.005).
Conclusion: This is the first electrophysiological study investigating swallowing abnormalities and subclinical dysphagia in MS patients with mild disability. The electrophysiological tests described in this study are useful to uncover subclinical dysphagia since they have the advantage of being rapid, easy to apply, non-invasive and without risk for the patients.
Disclosure: Nothing to disclose

P4211
A dual role of CCR5d32 polymorphism in multiple sclerosis

A. Bettencourt[1], A. Martins Silva[2], B. Leal[1], E. Santos[2], P.P Costa[3], B. Silva[1], S. Cavaco[4]
[1]Abel Salazar Institute of Biomedical Sciences, University of Porto – ICBAS/UP, Unit for Multidisciplinary Research in Biomedicine (UMIB), [2]Centro Hospitalar do Porto - Hospital Santo António, Neurology, [3]Instituto Nacional de Saúde Dr. Ricardo Jorge, [4]Centro Hospitalar do Porto, Neuropsychology Unit, Porto, Portugal

Background and aims: C-C chemokine receptor type-5 (CCR5), regulates both trafficking and effector functions of Th1 cells, macrophages, NK cells, and immature dendritic cells. A common 32-basepair deletion (CCR5delta32), in the coding region of CCR5 gene, originates a truncated non-functional receptor with reduced expression on the cell surface. The aim of this study was to investigate whether this deletion is associated with susceptibility and/or severity in Portuguese MS patients.
Methods or Materials or Case Report: A total of 500 MS patients and 230 controls were studied. A subset of 142 patients with disease duration of at least 10 years was divided into 2 groups according to severity: 100 patients were considered to have benign MS (EDSS≤3) and 42 aggressive MS (EDSS≥6). Kaplan-Meier survival analysis of the distribution of time to reach mild (EDSS=3) and severe disability (EDSS=6) was performed.
Results: No significant difference was observed in the allelic frequency of CCR5d32 between patients and controls (OR=0.659; p=0.054). Concerning disease severity, d32 frequency was significantly higher in the aggressive group (OR=4.000 p=0.002). For EDSS=3 as the end point, the median progression time was 6 years for d32carriers and 11 years for d32non-carriers (p=0.011). To reach an EDSS=6 the median progression time was 18 years for d32carriers and 23 years for the other group (p=0.039).
Conclusion: The 32 deletion may protect against the development of MS, although we could not confirm it in this study. However, once the disease is diagnosed, carriers seem to progress more rapidly to an advanced EDSS, suggesting a possible dual effect of this deletion.
Disclosure: Nothing to disclose

P4212

Neuromyelitis optica spectrum disorders with MOG-antibodies

D. Biotti[1], L. Mahieu[2], R. Bernard-Valnet[3], D. Peaureaux-Averseng[4], N. Fabre[5], M. Clanet[1], H. Dumas[6], F. Bonneville[7], R. Marignier[8], D. Brassat[1]
[1]Hopital PPR - CHU Purpan, Neurology, Toulouse, France, [2]Hopital PPR - CHU Purpan, Ophthalmology, Toulouse, France, [3]CHU Toulouse, Pôle Neuroscience, Neurology Department, Toulouse, France, [4]Hopital PPR - CHU Purpan, Neurology, toulouse, France, [5]Department of neurology, Toulouse University Hospital, France, Toulouse, France, [6]Department of neuroradiology, Toulouse University Hospital, France, Toulouse, France, [7]CHU Purpan, Neuroradiologie, toulouse, France, [8]Lyons, France

Background and aims: The presence (transient or persistent) of myelin-oligodendrocyte glycoprotein antibodies (MOG-Abs) has been reported in children during demyelinating neurological manifestations, particularly with acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS). In adults, MOG-Abs have been found in up to 30% of patients diagnosed with seronegative AQP4-Abs neuromyelitis optica spectrum disorders. When found, positive MOG-Abs allow earlier NMOSD diagnosis and treatment, increasing the odds for a better prognosis. Nevertheless, many questions remain about these MOG-Abs positive patients. The first short case-series published have highlighted several differences between AQP4+ and MOG-Abs + patients. In the latter group, caudal myelitis has been more frequently described and ophthalmological involvement (bilateral simultaneous optic neuritis) appears common. Attacks seem less frequent and severe than in seropositive AQP4-Abs patients. The therapeutic strategy in these patients remains to be defined.

Methods: Here, we present a series of 6 new seropositive MOG patients and compare them with 22 AQP4 +.

Results: 5 of the 6 were female, 2 experienced isolated bilateral optic neuritis, and 2 had a past history of myelitis and optic neuritis, 1 with relapsing optic neuritis and one with relapsing myelitis. Relapses were treated with high doses of steroids and/or PLEX. To prevent new relapse, all patients were treated with rituximab except for one who received Imurel because she was pregnant.

Conclusion: MOG antibodies appear as a new useful clinical biomarker. The identification of neuromyelitis optica spectrum disorders with MOG-antibodies should make discuss the rapid introduction of immuno active drugs.

Disclosure: Nothing to disclose

P4213

Avascular osteonecrosis in a cohort of MS patients treated with high dose methylprednisolone

M. Blinkenberg[1], T. Petersen[2], J.L. Frederiksen[3], P. Soelberg Sørensen[1], E.K. Narvestad[4], M. Ravnborg[5]
[1]Copenhagen University Hospital, Rigshospitalet, Danish MS Center, Department of Neurology, Copenhagen, Denmark, [2]Aarhus University, Deptartment of Neurology, Aarhus, Denmark, [3]Glostrup Hospital, University of Copenhagen, Clinic of Multiple Sclerosis and Optic Neuritis, Department of Neurology, Copenhagen, Denmark, [4]Copenhagen University Hospital, Rigshospitalet, Deptartment of Radiology, Copenhagen, Denmark, [5]Odense University Hospital, Department of Neurology, Odense, Denmark

Background and aims: Avascular osteonecrosis (AO) is considered to be a rare side effect to high cumulated doses of methylprednisolone (MP), although an unconfirmed study has reported increased prevalence (15.2%) in patients with multiple sclerosis (MS). Our aim was to determine the prevalence of AO in a well characterized cohort of MS patients, treated with monthly courses of high dose MP.

Methods: We studied 40 Danish patients from the international multicenter randomized controlled trial MECOMBIN. All patients started on interferon beta-1a and were afterwards randomized to tablets of MP 500mg daily for three days, once monthly, or placebo, for three to four years. We registered the total dose of MP, as well as fractures and hip joint pain and performed bilateral femoral magnetic resonance imaging (MRI) of the hips.

Results: 22 patients received MP and 18 placebo. Cumulated mean MP dose was 76.9±11.8g in the MP group and 5.5±10.2g the placebo group. Fractures were reported in two patients in the MP group and two in the placebo group. Hip pain was present in 10 patients in the MP group and in 7 patients in the placebo group (p=0.68). MRI revealed AO in one patient in the MP group and none in the placebo group.

Conclusion: The risk of AO is low in MS patients treated with high doses of MP, which does not corroborate previous findings. We found no increased risk of fractures or hip pain in patients receiving high cumulative doses of MP.

Disclosure: The study was supported by a grant form Biogen Idec

P4214

Sodium intake has no impact on MS disease activity: a study in 390 patients

B. Pignolet[1], B. Nassar[1], F. Bucciarelli[2], A. Naudin[1], F. Umuhoza[1], L. Scandella[3], N. Breuil[4], O. Outteryck[5], C. Lebrun-Frenay[6], H. Zephir[7], G.L. Defer[8], B. Brochet[9], M. Debouverie[10], P. Labauge[11], D. Laplaud[12], P. Clavelou[13], E. Thouvenot[14], C. Lubetzki[15], B. Fontaine[15], M. Clanet[16], P. Vermersch[17], J. de Seze[18], D. Brassat[16]

[1]CHU Toulouse, Toulouse, France, [2]Purpan, Toulouse, France, [3]chu toulouse, Toulouse, France, [4]chu toulouse, toulouse, France, [5]Chru Lille, Neurology, Lille Cedex, France, [6]Nice, France, [7]LILLE Cedex, France, [8]CHU Côte de Nacre, Neurology, Caen, France, [9]CHU Bordeaux, Bordeaux, France, [10]CHU Nancy, Nancy, France, [11]CHU Montpellier, Montpellier, France, [12]Nantes, France, [13]CHU Clermont-Ferrand, Clermont-Ferrand, France, [14]Nîmes, France, [15]Paris, France, [16]Toulouse, France, [17]Lille Cedex, France, [18]University Hospital Strasbourg, Neurology, Strasbourg, France

Background and aims: Salt consumption is suspected to play a role in MS disease activity. In vivo in mice, ex vivo in humans, and recently in a cohort of 50 MS patients, salt level seems to be associated with higher numbers of Th17 cells and a more severe disease course. In this study, we investigate the relationship between salt intake and MS disease severity with different severity criteria in 390 patients

Methods: Patients were included in the BIONAT cohort, a prospective phase IV observational multicentric study of 1200 Tysabri treated patients. In 390 we collected urine samples so as to calculate salt intake with the Tanaka formula. Disease severity was evaluated at baseline according to several definitions with the MSSS, various clinical and radiological criteria and response to Tysabri.

Results: A multivariate analysis did not show any association between salt consumption and disease severity

Conclusion: We were not able to confirm that high salt intake is associated with MS disease activity in the largest cohort of patients studied so far.

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P4215

Cyclophosphamide pulses therapy after natalizumab discontinuation in Multiple Sclerosis patients

M. Capobianco[1], M. Lo Re[2], F. Sangalli[3], L. Moiola[3], G. Comi[4], P. Perini[5], P. Gallo[6], M. Danni[7], L. Provinciali[7], A. Repice[8], L. Massacesi[8], F. Patti[9], S. Messina[9], A. Laroni[10], G.L. Mancardi[10], M. Calabrese[11], S. Monaco[11], E. Pucci[12], G. Giuliani[12], A. Bertolotto[1]

[1]AOU San Luigi Gonzaga, Orbassano, [2]Palermo, Italy, [3]Milan, [4]University Vita-Salute, Scientific Institute San Raffaele, Milan, [5]University of Padova, Padua, [6]Padua, [7]University of Ancona, Ancona, [8]Florence, [9]Catania, [10]University of Genova, Genoa, [11]University of Verona, Verona, Italy, [12]MA-Cerata, Italy

Background and aims: To collect data from patients with Multiple Sclerosis switching from natalizumab to cyclophosphamide. Natalizumab discontinuation induces the recurrence of MS disease activity: currently no therapeutic approach has been found able to abolish disease reactivation. Cyclophosphamide is an an alkylating agent that has been demonstrated to be effective in very aggressive forms of Multiple Sclerosis.

Methods: Data were collected from different Italian MS Centres and retrospectively evaluated from clinical records.

Results: In the early treatment group (washout period between natalizumab and cyclophosphamide less than 3 months), only 3/23 patients (13%) experienced a clinical relapse and only 2 out of 13 (15%) patients showed brain MRI activity at 3 months while none developed MRI activity at 6 months after cyclophosphamide introduction. In the Late Treatment Group (washout period between natalizumab and cyclophosphamide more than 3 months) 12/22 patients (54%) had relapses during the washout period and 4/22 (18%) after the introduction of cyclophosphamide; MRI disease activity was shown in 5/9 (55%) at 3 months and in 5/14 (35%) at 6 months after cyclophosphamide introduction.

Conclusion: These data show that cyclophosphamide could be able to reduce disease reactivation after natalizumab discontinuation, in particular with a short washout period after natalizumab discontinuation. It can be suggested that a short period (3-6 months) of cyclophosphamide monthly pulses could be used as "re-induction" treatment in this particular group of patients.

Disclosure: Nothing to disclose

P4216

Daclizumab high-yield process reduced disabling relapses and the rate of serious/severe relapses: post hoc analyses of the SELECT and DECIDE studies

L. Kappos[1], K. Selmaj[2], D.L. Arnold[3], E. Havrdova[4], A. Boyko[5], M. Kaufman[6], H. Wiendl[7], J. Rose[8], X. You[9], S. Shang[9], W. Castro-Borrero[9]

[1]University Hospital Basel, Basel, Switzerland, [2]Medical University of Lodz, Lodz, Poland, [3]NeuroRx Research and McGill University, Montreal, Canada, [4]First School of Medicine, Charles University in Prague, Prague, Czech Republic, [5]Russian Science & Research Medical University named after N. I. Pirogov and Moscow Multiple Sclerosis Center, Moscow, Russian Federation, [6]University of Tennessee - Knoxville, Cole Neurological Institute, Knoxville, TN, USA, [7]University of Münster, Münster, Germany, [8]University of Utah, Department of Neurology and the Neurovirology Research Laboratory, VASLCHCS, Salt Lake City, UT, USA, [9]Biogen Idec, Cambridge, MA, USA

Background and aims: To evaluate the frequency of disabling relapses and the rate of serious/severe relapses in patients with relapsing-remitting multiple sclerosis (RRMS) treated with daclizumab high-yield process (DAC HYP) versus placebo or interferon beta-1a (IFN beta-1a).

Methods: Data from SELECT and DECIDE studies of subcutaneous DAC HYP 150 mg once every 4 weeks and placebo (SELECT: DAC HYP, n=201; placebo, n=196) or intramuscular IFN beta-1a 30 mcg once weekly (DECIDE: DAC HYP, n=919; IFN beta-1a, n=922) were evaluated. Relapses leading to disability progression (disabling relapses) were defined as the onset of disability progression (≥1.0- or ≥1.5-point increase in EDSS score from a baseline EDSS score of ≥1.0 or 0.0, respectively, confirmed after 24 weeks) within 180 days following a relapse. The annualised rate of serious or severe relapses was evaluated based on relapses reported as severe/serious by the investigator.

Results: In SELECT at week 52, 1.0% of patients treated with DAC HYP experienced disabling relapses versus 6.6% of patients treated with placebo (P=0.0032; Table). In DECIDE at end of treatment period visit, 2.9% of DAC HYP-treated patients experienced disabling relapses versus 5.8% of patients treated with IFN beta-1a (P=0.0031). DAC HYP treatment reduced the annualised rate of serious and severe relapses by 67% versus placebo (P<0.0001) and by 38% versus IFN beta-1a (P=0.0021; Table).

	SELECT (n=397)		DECIDE (n=1841)	
	DAC HYP (n=201)	Placebo (n=196)	DAC HYP (n=919)	IFN beta-1a (n=922)
Number of patients with disabling relapses, n (%)[a]	2 (1.0)[1]	13 (6.6)	27 (2.9)[2]	53 (5.8)
Number of patients with a serious or severe relapse, n (%)[b]	19 (9.5)	43 (21.9)	100 (10.9)	131 (14.2)
Annualised rate (95% CI) of serious or severe relapses	0.096 (0.061, 0.149)	0.294 (0.226, 0.383)	0.081 (0.065, 0.101)	0.130 (0.106, 0.160)
Rate ratio (95% CI)	0.325 (0.196, 0.539)[3]	—	0.621 (0.458, 0.841)[4]	—

CI, confidence interval; DAC HYP, daclizumab high-yield process; EDSS, expanded disability status scale.
[a]Disabling relapses defined as onset of disability progression (≥1.0- or ≥1.5-point increase in EDSS score from a baseline EDSS score of ≥1.0 or 0.0, respectively, confirmed after 24 weeks) within 180 days following a relapse
[b]Serious or severe relapse as defined by the investigator.
[1]*P*=0.0032 when comparing 150 mg DAC HYP with Placebo by Fisher's exact test.
[2]*P*=0.0031 when comparing 150 mg DAC HYP with 30 mcg IFNbeta-1a by Chi-squared test.
[3]*P*<0.0001 when comparing 150 mg DAC HYP with Placebo estimated from a poisson regression adjusted for baseline EDSS (≤2.5 vs >2.5), baseline age (≤35 vs >35), and number of relapses in the 1 year prior to study entry.
[4]*P*=0.0021 when comparing 150 mg DAC HYP with IFNbeta-1a estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (≤2.5 vs >2.5) and baseline age (≤35 vs >35).

Effect of DAC HYP on Disabling Relapses and the Rate of Serious and Severe Relapses

Conclusion: DAC HYP reduced the proportion of patients with disabling relapses and the rate of serious or severe relapses compared with placebo and IFN beta-1a.

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P4217

Effect of fingolimod on the revised, more comprehensive measure of no evidence of disease activity and worsening (NEDA-4) at 12 and 24 months

L. Kappos[1], E.-W. Radue[2], T. Sprenger[1], E. Havrdova[3], M. Freedman[4], B. Cree[5], M.P. Sormani[6], N. Sfikas[7], N. Bergvall[7], D. Piani Meier[7], D. Tomic[7], N. De Stefano[8]
[1]University Hospital Basel, Basel, Switzerland, [2]Medical Image Analysis Center (MIAC), University Hospital, Basel, Basel, Switzerland, [3]Department of Neurology, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [4]Ottawa Hospital, Multiple Sclerosis Research Clinic, Ottawa, USA, [5]University of California San Francisco, Department of Neurology, San Francisco, USA, [6]University of Genoa, Biostatistics Unit, Department of Health Sciences, Genoa, Italy, [7]Novartis Pharma AG, Basel, Switzerland, [8]University of Siena, Sienna, Italy

Background and aims: Current definitions of 'No Evidence of Disease Activity and worsening' (NEDA) in patients with relapsing MS (RMS) are based on assessment of EDSS progression, relapses, and active MRI lesions, but the MRI metric depicts mainly focal activity and less so outcomes related to diffuse damage such as brain volume loss (BVL). This study evaluates the impact of including BVL in a four-measure definition of NEDA, e.g. NEDA-4.
Methods: Pooled data of patients receiving fingolimod 0.5 mg or placebo from two phase 3 trials (FREEDOMS/FREEDOMS II) were compared. NEDA-4 was defined as: no confirmed relapses, no 6-month confirmed disability progression, no new/enlarging T2-lesions and annual BVL (using SIENA method) less than 0.4%. This BVL cut-off corresponds to approximately twice the average rate in non-MS individuals (0.1%–0.3%) but remains below the range of mean rates typically seen in MS patients (0.5%–1.35%). NEDA-4 was compared for fingolimod vs. placebo at months (M) 12 and 24.
Results: Significant (p<0.0001) difference (OR, 95% CI) in NEDA-4 status vs. placebo was observed, M12: 26.5% vs. 8.7%, 3.77 (2.77−5.12); M24: 19.7% vs. 5.3%, 4.41 (3.03−6.42). In patients with high disease activity despite treatment with disease modifying therapies in the past year, effects were comparable (Table). Similar results observed with other BVL cut-offs (0.2%–1.2%).

	Month-12			Month-24		
	Fingolimod 0.5 mg N=240	Placebo N=250	Treatment effect vs. placebo OR (95% CI), p-value[7]	Fingolimod 0.5 mg N=240	Placebo N=250	Treatment effect vs. placebo OR (95% CI), p-value[7]
Proportion of patients achieving NEDA-4[6]	25.8%	8.2%	3.90 (2.23- 6.81) p<0.0001	20.5%	3.9%	6.35 (3.02–13.35) p<0.0001

[*]**high disease activity**: equal/more relapses in the year before the study than in the previous year, or =1 relapse in the year before the study and =1 Gd+ lesions, or =9 T2 lesions at baseline

[6]**NEDA-4**: no confirmed relapses, no 6-month confirmed disability progression (an increase of 1.5 points from a baseline EDSS score of 0.0 or an increase of 1.0 point from a baseline EDSS score of = 1.0), no new/enlarging T2-lesions and annual BVL less than 0.4%

[7]OR and corresponding p-value were derived from logistic regression of NEDA on treatment. OR of 1.00 signifies no treatment effect vs. comparator

BVL, brain volume loss; **CI**, confidence interval; **NEDA**, no evidence of disease activity; **OR**, Odds ratio

Table: NEDA-4 status, by treatment in subgroup of patients who had high disease activity despite treatment with disease modifying therapies*

Conclusion: Significantly more fingolimod-treated patients achieved NEDA-4 versus placebo at both time-points. By integrating measures of both focal and diffuse damage, NEDA-4 may provide a more comprehensive assessment of disease activity and worsening in RMS.
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P4218

INSPIRE: standardized acquisition and centralized quantitative MRI evaluation of RRMS patients in German daily clinical practice

A. Gass[1], J. Würfel[2], J. Gregori[3], S. Hoffmann[3], A. Fuchs[4], C. Cornelissen[4]

[1]University Hospital Mannheim, Neurology, Mannheim, Germany, [2]University Medicine Goettingen, Institute of Neuroradiology, Göttingen, Germany, [3]mediri GmbH, Heidelberg, Germany, [4]Novartis Pharma GmbH, Nuremberg, Germany

Background and aims: INSPIRE is a non-interventional nationwide German study, to validate the feasibility and potential benefit of standardized MR-acquisition and central-quantitative MR-reading in RRMS-patients. MRI has become an integral part of MS patient-management. However, quantitative analyses e.g. of the lesion-load is not trivial and has been realized nearly exclusively in clinical trials. We here investigate whether additional quantitative information and visualization of the lesion-load gives added value to the daily management of RRMS-patients.

Methods: This NIS will include 250 patients derived from 30 centers. Sites underwent expert training and implementation of standardized MRI-sequences. In addition to routine local diagnostic reading, a centralized quantitative MRI-data analysis is performed (volume of T2w-lesions, T1w-hypointense and contrast-enhancing lesions, percentage of brain volume change via boundary shift integral). The results are visualized and provided to the physicians.

Results: First patient visit was in June 2014. We present the study design and the procedures for quality assurance, MRI-protocols and the centralized quantitative MR-analysis. Baseline characteristics and MRI-results of the first 100 patients will be provided. Data are analyzed in regard to: 1. feasibility of the proposed MRI-algorithm (site set-up, sequence implementation, embedding in a routine radiological work-flow, data management, communication of centralized analysis results). 2. MRI-data quality and stability (consistency, artifacts, signal-to-noise-ratio, contrast-to-noise-ratio). 3. usefulness for clinical patient management.

Conclusion: A more sophisticated, additional quantitative MRI-analysis is provided in a real world situation. Presentation of quantiative data on T2w-lesion count and volumes as well as the visualization of MRI-abnormalities provide additional information to the treating neurologist and support patient management.

Disclosure: This study is supported by the Novartis Pharma GmbH, Nuremberg, Germany

P4219

Natalizumab (NA) in pediatric multiple sclerosis (MS): results of the Italian registry

A. Ghezzi[1], L. Moiola[2], C. Pozzilli[3], V. Brescia Morra[4], P. Gallo[5], L.M.E. Grimaldi[6], P. Annovazzi[1], M. Filippi[7], G. Comi[2]

[1]Gallarate, Italy, [2]Milan, Italy, [3]Rome, Italy, [4]Federico II University, Neurosciences, Reproductive and Odontostomatological Sciences , Naples, Italy, [5]Padua, Italy, [6]Fondazione Istituto San Raffaele "G. Giglio" di Cefalù, Unità Operativa Neurologia, Cefalù, Italy, [7]Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Neuroimaging Research Unit, Milan, Italy

Background and aims: NA is a promising option for ped-MS patients with active MS and a poor response to IFNB and GA but data are not available in large cohorts and after a long-term follow up. Our study has been carried out to provide further information on this topic.

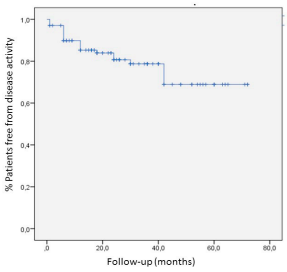
Methods: A registry was established in 2007 in Italy to collect cases treated with NA before 18 years of age. 23 MS Italian centres participated to this study

Results: 101 patients were included (69 females), mean age of MS onset 12.9±2.7 years, mean age at NA initiation 14.7±2.4 years. Mean treatment duration was 34.2±18.3 months.

A total of 15 relapses were recorded in 9 patients, annualized relapse rate was 2.3±1.0 in the year prior to NA and decreased to 0.1±0.3 ($p<0.001$) at last NA infusion.

Mean EDSS decreased from 2.6±1.3 at initiation of NA to 1.8±1.2 at the time of last visit ($p<0.001$). New lesions on T2 or Gd+ were observed in 10/91 patients after 6 months, in 6/87 after 12 months, in 2/61 after 18 months, in 2/68after 24 months, in 3/62 after 30 months, in 5/43 after a longer follow up. At the time of last observation 64% of patients were free from clinical (relapses/increased EDSS) and/or MRI activity (figure)

No relevant adverse events were recorded.



Conclusion: A relevant reduction of relapse rate and EDSS was observed after NA treatment, compared to pre-treatment period. NEDA (No evidence of disease activity) occurred in about 65% of cases.

Disclosure: Nothing to disclose

P4220

Long-term follow-up of the effect of delayed-release dimethyl fumarate on No Evidence of Disease Activity in patients with multiple sclerosis

G. Giovannoni[1], E. Havrdova[2], R. Gold[3], R.J. Fox[4], L. Kappos[5], J.T. Phillips[6], A. Zhang[7], N.C. Kurukulasuriya[7]
[1]Blizard Institute, Queen Mary University of London, London, United Kingdom, [2]Department of Neurology, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [3]St. Josef Hospital, Ruhr University, Bochum, Germany, [4]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, USA, [5]University Hospital, Basel Neurology, Basel, Switzerland, [6]Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, USA, [7]Biogen Idec, Inc., Cambridge, USA

Background and aims: ENDORSE is an 8-year extension of DEFINE/CONFIRM studying long-term effects of delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) in relapsing-remitting multiple sclerosis. In this post hoc analysis, we report annual no evidence of disease activity (NEDA) outcomes.

Methods: Patients randomised to DMF 240 mg twice (BID) or three times daily (TID) in DEFINE/CONFIRM continued same dosage in ENDORSE; patients randomised to placebo (PBO) or glatiramer acetate (GA) were re-randomised 1:1 to DMF BID or TID. Patients who fulfilled the following criteria (measured annually) were considered to have NEDA: no relapses, no 24-week Expanded Disability Status Scale–confirmed progression, no gadolinium-enhanced lesions, and no new/enlarging T2 lesions. Data for DMF BID (as of 14 May 2014) are reported.

Results: Of 1,736 ENDORSE patients, 746 had efficacy assessments; 363 received DMF BID (211 BID/BID, 104 PBO/BID, 48 GA/BID). For BID/BID patients, proportions with NEDA during Years 1 and 2 (DEFINE/CONFIRM) and Years 3, 4, and 5 (ENDORSE) were 37.9%, 50.2%, 47.9%, 52.0%, and 42.5%, respectively. For PBO/BID, corresponding proportions with NEDA were 21.2%, 25.0%, 23.1%, 42.5%, and 43.2%, respectively. For GA/BID, corresponding proportions with NEDA were 16.7%, 27.1%, 33.3%, 45.5%, and 31.6%, respectively. Absence of measured clinical activity and of measured magnetic resonance imaging (MRI) activity outcomes are presented below (Table).

Table. Proportion of patients with absence of measured clinical and MRI activity by yearly interval

Proportion of patients, n/N (%)	Continued DMF[a]	New to DMF[a]	
	BID/BID	PBO/BID	GA/BID
Absence of Measured Clinical Activity[b,c]			
Year 0-1 (DEFINE/CONFIRM Year 1)	401/501 (80.0)	170/249 (68.3)	86/118 (72.9)
Year 1-2 (DEFINE/CONFIRM Year 2)	406/501 (81.0)	177/249 (71.1)	91/117 (77.8)
Year 2-3 (ENDORSE Year 1)	431/501 (86.0)	208/249 (83.5)	96/118 (81.4)
Year 3-4 (ENDORSE Year 2)	402/468 (85.9)	177/206 (85.9)	88/100 (88.0)
Year 4-5 (ENDORSE Year 3)	381/443 (86.0)	173/192 (90.1)	71/84 (84.5)
Absence of Measured MRI Activity[d,e]			
Year 0-1 (DEFINE/CONFIRM Year 1)	94/210 (44.8)	29/104 (27.9)	13/48 (27.1)
Year 1-2 (DEFINE/CONFIRM Year 2)	129/205 (62.9)	29/86 (33.7)	18/44 (40.9)
Year 2-3 (ENDORSE Year 1)	118/189 (62.4)	29/68 (42.6)	19/39 (48.7)
Year 3-4 (ENDORSE Year 2)	120/183 (65.6)	44/64 (68.8)	21/36 (58.3)
Year 4-5 (ENDORSE Year 3)	95/153 (62.1)	37/56 (66.1)	17/30 (56.7)

[a]DMF, delayed-release DMF (also known as gastro-resistant DMF); [b]Analysis performed in intent-to-treat population; [c]Defined as no relapses and no 24-week Expanded Disability Status Scale–confirmed progression; [d]Analysis performed in MRI cohort; [e]Defined as no gadolinium-enhanced lesions and no new/enlarging T2 lesions.

Conclusion: Favourable NEDA outcomes were maintained throughout 5 years with continuous DMF treatment; average NEDA rates over time were higher with early versus delayed DMF treatment. PBO/BID and GA/BID patients demonstrated improved NEDA after switching to DMF.

Disclosure: Study supported by: Biogen Idec

P4221

Multiple sclerosis and social networks

A.-K. Göcke[1], A. Tallner[2], M. Mäurer[1]
[1]Caritias Krankenhaus Bad Mergentheim, Neurology, Würzburg, Germany, [2]Institut für Sport und Sportwissenschaften, Erlangen, Germany

Background and aims: Modern electronic technologies and social networks have created a huge community of internet users. In Germany >75% of the general population has internet access and the „World Wide Web" has become the most important source for health issues. Therefore we evaluated the role of social networks for health issues of MS patients.

Methods: We sent out questionaires to 1554 MS Patients registered in our database. 486 individuals returned the questionnaires (32%). Questionnaires comprise questions about disease course and symptoms, internet usage (hardware, frequency, preferences) as well as depression and quality of life.

Results: 89% of our cohort indicates to use the PC to access the world wide web, 56% use smartphones, but only 26% tablet computers. 52% of our patients use social networks, and more than 60% report a daily use. Among the social networks Facebook is by far the most popular platform, other providers like Xing, Instagram or Twitter are of minor importance. In addition only a minority of patients read private MSBlogs.

Although a high proportion of MS patients use social networks only a minority join MS support groups on social platforms (12%) and take part in MS assistant services delivered via the Internet (4%).

Conclusion: A high proportion of MS patients use social networks, in particular facebook. Actually health issues are not a primary reason to join a social network. Due to the intensive usage of social networks we believe that these networks should become an important tool for MS care centers in order to deliver health education.

Disclosure: Nothing to disclose

P4222

Predictors of suicidal ideation in patients feeling severely affected by multiple sclerosis

H. Golla[1], J. Strupp[1], C. Ehmann[1], M. Galushko[1], R. Bücken[1], S. Hamacher[2], H. Pfaff[3], R. Voltz[1]
[1]University Hospital Cologne, Department of Palliative Medicine, Cologne, Germany, [2]University Hospital Cologne, Institute of Medical Statistics, Informatics and Epidemiology, Cologne, Germany, [3]University Hospital Cologne, Institute of Medical Sociology, Health Services Research, Cologne, Germany

Background and aims: Being severely affected by Multiple Sclerosis (MS) brings substantial physical and psychological challenges. Contrary to the commonly held notion that MS is not a lethal disease, it can lead to death and is reflected in alarming rates of assisted suicide and euthanasia among patients.

Analysis of independent variables promoting suicidal ideation in severely affected MS patients stating suicidal thoughts.

Methods: A self-report questionnaire with 25 needs categories including one item "prone to suicidal ideation" was applied. Connections between risk factors were tested with Spearman's rank correlation. Relevant covariates showing a p-value <0.05 in the univariate analysis and remaining in the multivariable logistic regression model after stepwise, backward selection procedure were included in the final model.

Results: 573 patients completed the questionnaire. Median age was 51 years (range 20-83), 66.8% were female. 42.6% suffered from secondary progressive, 24.7% from relapsing-remitting and 21.9% from primary progressive MS. 22.1% had suicidal ideation. A set of six statistically significant criteria for suicidal ideation were found. Three items were predictors for suicidal ideation: the extent to which MS affects leisure time ($p<0.001$), depression ($p<0.000$), and feeling socially excluded ($p<0.002$). Three items reduced the odds of suicidal ideation: having a purpose in life ($p<0.000$), being productive ($p<0.000$), and having comfort in faith and spiritual beliefs ($p<0.024$).

Conclusion: We identified several potentially modifiable factors that may help preventing suicide in people with MS. Integrating Palliative Care with its multidisciplinary approach might be important to reduce patients' burden.

Disclosure: The study was funded by the "Gemeinnützige Hertie-Stiftung" (grant # 1.01.1/06/009).

P4223

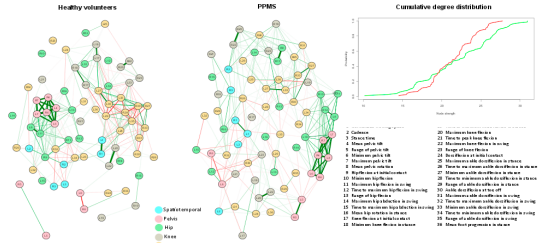
The configuration of gait temporal joint patterns is changed in patients with primary progressive multiple sclerosis: network and random forest analysis

D. Gómez Andrés[1], I. Pulido-Valdeolivas[1], I. González-Suárez[2], J.A. Martín-Gonzalo[3], I. Rodríguez-Andonaegui[3], C. Oreja-Guevara[2], E. Rausell[1]
[1]*Universidad Autónoma de Madrid, Anatomy, Histology and Neuroscience, Madrid, Spain,* [2]*Hospital Universitario Clínico San Carlos, Neurology, Madrid, Spain,* [3]*Physiotherapy School. ONCE-UAM, Madrid, Spain*

Background and aims: Efficient gait relies on the ability of the central nervous system to command a system of sequential muscle synergy chains to manage weight support and translation, by setting gait cycle time-specific joint angle configurations. These switch in patients with primary progressive multiple sclerosis (PPMS) as an adaptive response to maintain propositive gait. Our aims are to define which gait parameters switch from normal configuration to a more adaptive one and to assess the system's global plasticity using random forest and network analysis respectively.

Methods: 72 kinematic/spatiotemporal parameters (36left/36right) of 5 joints were acquired by instrumented gait analysis from 4-5 gait cycles (10 PPMS patients/12 healthy volunteers). Random forests were trained to define classifier parameters for PPMS or healthy condition (goodness-of-fit assessment =1-OOB error rate). The influence of each predictor was estimated by mean percentage of decrease in model accuracy when variable is out-of-the-bag. Two networks were generated (nodes=gait parameters, edge weight = bivariate Spearman's correlation coefficients between nodes) and their properties and parameter organization (building-blocks) were assessed according to Rubinov and Sporns, 2010.

Results: PPMS patients' walking strategies differ from normal by more flexed knee at initial contact (leading frecuently to recurvatum in stance), longer stance time, lower cadence and abnormal minimum hip flexion (goodness-of-fit=95.7%), which reflects a poor distal joint support. PPMS gait system is rearranged to maintain maximum control of pelvic-femoral joints by setting more distributed relationships with ankle/knee parameters.



Networks and cumulative distribution of node strength

Conclusion: New gait joint configurations are provided by plastic adaptation to the constraints imposed by brain damage in PPMS.

Disclosure: Nothing to disclose

P4224

Cervical cord atrophy in clinically isolated syndrome and early multiple sclerosis: a novel paraclinical risk marker for conversion to manifest multiple sclerosis?

I. Hagström[1], B. Bellenberg[1], R. Schneider[2], A. Salmen[2], F. Weiler[3], R. Gold[2], C. Lukas[1]
[1]*Ruhr-University Bochum, Radiology, Bochum, Germany,* [2]*Ruhr-University Bochum, Neurology, Bochum, Germany,* [3]*Fraunhofer Mevis, Bremen, Bremen, Germany*

Background and aims: Cervical cord atrophy predictive for disability progression in manifest Multiple Sclerosis (MS). We aimed to quantify and evaluate the clinical impact of atrophy of the upper cervical cord area (UCCA) in early MS and to assess differences between patients assigned clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS). We compared UCCA in CIS patients converting to RRMS within 2 years with patients with stable CIS.

Methods: 45 CIS patients, 48 RRMS and 34 matched healthy controls underwent 3D-T1-weighted brain MR-imaging at 3 Tesla covering the cervical cord. UCCA was quantified by a semi-automated volumetric method between the C1 and C3 level. Clinical examination included the expanded disability status scale (EDSS), 9-hole peg test (9HPT) and disease duration.

Results: Although all patients had low EDSS and short disease durations at baseline (table 1), significant UCCA atrophy was detected in the entire group, driven by RRMS and CIS patients, who converted to RRMS during follow-up (figure 1). In the entire group and in RRMS, UCCA correlated significantly with the pyramidal functional system score, the 9HPT score and by trend with EDSS (table 2). In converting CIS patients, a trend for correlation of UCCA to 9HPT was observed.

	healthy controls	all patients	all CIS	remaining CIS at follow-up	CIS converting to RRMS	RRMS
N (m/f)	34 (14/20)	93 (30/63)	45 (16/29)	31 (13/18)	14 (3/11)	48 (14/34)
age/years	41.6+-14.7	36.0+-11.3	33.5+-9.4	34.5+-9.2	31.4+-10.0	38.3+-12.4
disease duration /month	-	9.3+-8.6	5.5+-6.1	4.5+-5.0	7.8+-7.8	12.8+-9.2 *P<0.001*[b]
EDSS	-	2.0 [0-4]	1.5 [0-3.5]	1.5 [0-3.5]	1.5 [0-3.5]	2 [0-4]
UCCA /mm²	82.0+-6.5	77.8+-8.7 *P=0.013*[a]	79.3+-8.4	80.7+-8.1	76.4+-8.7a *P=0.018*[a]	76.5+-8.9a *P=0.003*[a]

[a] significant difference between patient groups and controls by t-test; [b] significant difference between RRMS and CIS by t-test; age, disease duration, UCCA: mean+-SD, EDSS: median [range]

Table 1: Demography and clinical parameters in the study groups

	All patients	remaining CIS at follow-up	CIS converting to RRMS	RRMS
	Spearman's rho / P			
EDSS	n.s. -0.247 / 0.054	n.s.	n.s.	n.s. -0.247 / 0.094
Pyramidal EDSS subscore	* -0.249 / 0.020	n.s.	n.s.	* -0.350 / 0.018
9-hole peg test score	* 0.274 / 0.008	n.s.	n.s. 0.464 / 0.095	* 0.329 / 0.024

Table 2: Spearman correlation analyses of UCCA related to disability scores

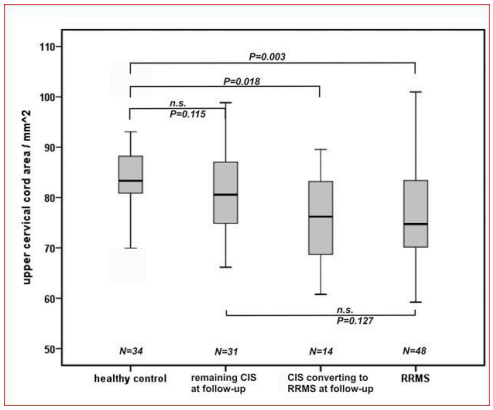


Figure 1: UCCA in different groups (boxes: median / interquartile range, error bars: minimum / maximum); significance of group differences by t-tests; n.s.: not significant

Conclusion: UCCA atrophy was related to 9HPT performance and pyramidal symptoms in early MS. We found evidence, that CIS patients converting to MS during 2 years follow-up can be differentiated from stable CIS patients by UCCA atrophy at baseline. The predictive value of cord atrophy for conversion to MS should be addressed in further longitudinal studies.

Disclosure: This work was supported by the German Federal Ministry for Education and Research, BMBF, German Competence Network Multiple Sclerosis (KKNMS), grant no. 01GI0914.

P4225

Superior efficacy of alemtuzumab on disability outcomes versus subcutaneous interferon beta-1a in treatment-naïve multiple sclerosis patients using the SAD-plus composite endpoint

X. Montalban[1], J.A. Cohen[2], H.-P. Hartung[3], E. Havrdova[4], D.H. Margolin[5], L. Kasten[6], E.J. Fox[7]

[1]Vall d'Hebron University Hospital, Barcelona, Spain, [2]Cleveland Clinic, Cleveland, Cleveland, USA, [3]Heinrich-Heine-University, Düsseldorf, Germany, [4]First Medical Faculty, Charles University in Prague, Prague, Czech Republic, [5]Genzyme, a Sanofi company, Cambridge, USA, [6]PROMETRIKA LLC, Cambridge, USA, [7]Central Texas Neurology Consultants, Round Rock, USA

Background and aims: Expanded Disability Status Scale (EDSS) score may not be sensitive enough to detect meaningful changes in neurological function in some relapsing-remitting multiple sclerosis (MS) patients. Here, we present a novel composite endpoint to examine disability outcomes in the CARE-MS I study (NCT00530348).

Methods: Treatment-naïve patients received 2 courses of alemtuzumab 12mg, or subcutaneous interferon beta-1a (SC IFNB-1a) 44μg 3 times/week for 2 years. Sustained accumulation of disability (SAD) was defined as ≥1.0-point increase in EDSS sustained over 6 months (≥1.5 point if baseline EDSS=0). Post hoc disability outcomes included 6-month sustained worsening on the following measures: Timed 25-Foot Walk (T25FW; 20% increase from baseline), 9-Hole Peg Test (9-HPT; 20% increase), or Sloan visual acuity at 2.5% contrast (7-letter worsening). Sustained worsening on any disability measure (T25FW, 9-HPT, Sloan, or SAD) was assessed (SAD-plus).

Results: Alemtuzumab (N=376) significantly reduced the risk of 6-month confirmed accumulation of disability, measured by SAD-plus, as compared with SC IFNB-1a (n=187). The proportion of patients achieving the composite SAD-plus endpoint was 33% lower with alemtuzumab than SC IFNB-1a (30.4% vs 41.8%; P=0.0210). Treatment effects on each component measure were directionally similar but not statistically significant: SAD (8.0% vs 11.1%; P=0.22), worsening on T25FW (8.3% vs 9.0%; P=0.76), 9-HPT (4.0% vs 6.3%; P=0.27), or Sloan (11.2% vs 17.3%; P=0.11).

Conclusion: SAD-plus is more sensitive to clinically meaningful impairments than EDSS-based SAD alone. Post hoc analysis of this endpoint in CARE-MS I demonstrates alemtuzumab's superior effect on disability relative to SC IFNB-1a in treatment-naïve patients with relapsing MS.

Disclosure: Study supported by Genzyme, a Sanofi company, and Bayer Healthcare Pharmaceuticals.